



1
00:00:01,200 --> 00:00:05,066
[musical tones]
[electronic sounds of data]

2
00:00:17,833 --> 00:00:19,400
- Welcome to the last talk

3
00:00:19,400 --> 00:00:23,900
of the 2015
NASA Ames Summer Series.

4
00:00:23,900 --> 00:00:26,666
We began the series
with a talk entitled

5
00:00:26,666 --> 00:00:30,000
"Brain Function Through
the Eyes of the Beholder"

6
00:00:30,000 --> 00:00:32,166
by Dr. Lee Stone.

7
00:00:32,166 --> 00:00:36,466
We went through a journey where
we looked at earth science,

8
00:00:36,466 --> 00:00:39,066
materials needed for reentry,

9
00:00:39,066 --> 00:00:42,433
science fiction on Mars.

10
00:00:42,433 --> 00:00:44,900
We also had talks as far

11
00:00:44,900 --> 00:00:49,566
from the Vatican Observatory.

12

00:00:49,566 --> 00:00:53,166

And so we went through different stages of what NASA does

13

00:00:53,166 --> 00:00:55,633

and what we see in the world.

14

00:00:55,633 --> 00:00:58,633

Today's talk entitled

15

00:00:58,633 --> 00:01:01,733

"Fractal-Based Mapping of Vascular Patterning

16

00:01:01,733 --> 00:01:03,766

for Human Space Exploration"

17

00:01:03,766 --> 00:01:08,066

will talk about visualization and, specifically,

18

00:01:08,066 --> 00:01:13,300

when we can visualize processes, we can understand them better.

19

00:01:13,300 --> 00:01:17,866

By understanding them, we could approach risk mitigation,

20

00:01:17,866 --> 00:01:23,433

and we could also look at new futures.

21

00:01:23,433 --> 00:01:26,900

The talk will be given by Dr. Patricia Parsons.

22

00:01:28,866 --> 00:01:31,233

Dr. Parsons received a Bachelor's

23

00:01:31,233 --> 00:01:34,400
in Science and Engineering
from the University of Michigan

24

00:01:34,400 --> 00:01:37,266
in 1983.

25

00:01:37,266 --> 00:01:41,233
She then continued her education
and received a Master's

26

00:01:41,233 --> 00:01:42,733
in Science
and Chemical Engineering

27

00:01:42,733 --> 00:01:47,500
from Case Western University
in 1989

28

00:01:47,500 --> 00:01:49,500
and a PhD
in chemical engineering

29

00:01:49,500 --> 00:01:53,166
from John Hopkins University
in '92.

30

00:01:53,166 --> 00:01:56,400
She joined
NASA Glenn Research Center

31

00:01:56,400 --> 00:02:00,600
in 2001
as a biomedical engineer

32

00:02:00,600 --> 00:02:04,900
and joined Ames now in 2014.

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00:02:04,900 --> 00:02:07,733

She is the lead innovator

34

00:02:07,733 --> 00:02:11,933

for NASA's VESGEN software.

35

00:02:11,933 --> 00:02:15,566

In this talk,

she will describe VESGEN,

36

00:02:15,566 --> 00:02:17,100

the process,

37

00:02:17,100 --> 00:02:20,766

and how it could be applied

for space exploration.

38

00:02:20,766 --> 00:02:24,566

Please join me

in welcoming Dr. Parsons.

39

00:02:24,566 --> 00:02:27,566

[applause]

40

00:02:37,633 --> 00:02:40,166

- Thank you, Dr. Cohen,

for your kind introduction,

41

00:02:40,166 --> 00:02:45,333

for the opportunity

to present our research today.

42

00:02:45,333 --> 00:02:49,000

Complex, fractally branching

vascular systems

43

00:02:49,000 --> 00:02:52,766

are essential for all

higher life forms on Earth,

44

00:02:52,766 --> 00:02:55,833

including humans,
other vertebrates,

45

00:02:55,833 --> 00:02:59,333

insects, and plants.

46

00:02:59,333 --> 00:03:02,533

Vascular systems in our body

47

00:03:02,533 --> 00:03:05,000

perform the distributed
communication

48

00:03:05,000 --> 00:03:07,433

of essential metabolic
and other factors

49

00:03:07,433 --> 00:03:11,900

between widely separated,
specialized cells,

50

00:03:11,900 --> 00:03:14,900

tissues, organs,

51

00:03:14,900 --> 00:03:19,000

such as the heart,
brain, and skin.

52

00:03:19,000 --> 00:03:22,733

In humans, for example,
every cell in our body

53

00:03:22,733 --> 00:03:26,966

must reside
within approximately 500 microns

54

00:03:26,966 --> 00:03:29,666

of a small fragile

capillary vessel

55

00:03:29,666 --> 00:03:33,800

to obtain
necessary life support.

56

00:03:33,800 --> 00:03:36,400

Downstream of our single--

57

00:03:36,400 --> 00:03:38,866

of our single pumping hearts,

58

00:03:38,866 --> 00:03:42,833

approximately
40 branching generations

59

00:03:42,833 --> 00:03:46,100

of successively
tapering vessels

60

00:03:46,100 --> 00:03:48,933

connect down
to these tiny capillaries

61

00:03:48,933 --> 00:03:50,400

that are the only site

62

00:03:50,400 --> 00:03:53,100

performing
the vascular transfer functions

63

00:03:53,100 --> 00:03:56,333

of exchanging the metabolic,
immune, reproductive,

64

00:03:56,333 --> 00:03:59,900

and other factors
that we utilize in our bodies.

65

00:04:01,833 --> 00:04:04,866
Our research discovery story

66

00:04:04,866 --> 00:04:10,433
started with my experimental
observations at the microscope

67

00:04:10,433 --> 00:04:12,733
at the University of Washington,

68

00:04:12,733 --> 00:04:16,466
where I was a postdoc
and then junior faculty.

69

00:04:16,466 --> 00:04:19,466
What I observed
that was surprising to me

70

00:04:19,466 --> 00:04:22,533
was that every major regulator

71

00:04:22,533 --> 00:04:25,400
of vascular remodeling
and growth

72

00:04:25,400 --> 00:04:29,800
induced a specific,
unique fingerprint

73

00:04:29,800 --> 00:04:33,466
or signature vascular pattern.

74

00:04:33,466 --> 00:04:38,233
So these observations
suggested--

75

00:04:38,233 --> 00:04:41,300
the plausible
long-term hypothesis

76

00:04:41,300 --> 00:04:44,033

we continue to pursue
in our research

77

00:04:44,033 --> 00:04:46,700

is that vascular patterns
can provide us

78

00:04:46,700 --> 00:04:48,733

with relatively accessible

79

00:04:48,733 --> 00:04:50,800

but integrative readouts

80

00:04:50,800 --> 00:04:54,400

of complex dominant
molecular signaling,

81

00:04:54,400 --> 00:04:56,633

because as my
space biology colleagues

82

00:04:56,633 --> 00:04:58,566

know much better than I do,

83

00:04:58,566 --> 00:05:02,533

these molecular signaling
pathways are complex

84

00:05:02,533 --> 00:05:06,233

and really require
the modern omics revolution

85

00:05:06,233 --> 00:05:08,466

to begin to dissect.

86

00:05:12,266 --> 00:05:14,066

So...

87

00:05:14,066 --> 00:05:16,866

when faced...

88

00:05:16,866 --> 00:05:19,833

with the bewildering,
amazing variety

89

00:05:19,833 --> 00:05:22,566

of vascular systems
and the various species,

90

00:05:22,566 --> 00:05:25,433

tissues, length scales,

91

00:05:25,433 --> 00:05:29,033

one unifying principle

92

00:05:29,033 --> 00:05:31,600

that we really can hang on to

93

00:05:31,600 --> 00:05:35,866

is the usefulness
of fractal branching

94

00:05:35,866 --> 00:05:39,400

as a natural
space-filling mechanism

95

00:05:39,400 --> 00:05:41,566

in physiology.

96

00:05:45,533 --> 00:05:47,566

Our research story did start

97

00:05:47,566 --> 00:05:52,000

with the avian chorioallantoic
membrane, or CAM.

98

00:05:52,000 --> 00:05:54,266

That was the research
in which I developed

99

00:05:54,266 --> 00:05:58,500

the initial observations.

100

00:05:58,500 --> 00:06:01,300

Then,
as funded by NIH and NASA,

101

00:06:01,300 --> 00:06:04,966

we extended these observations
into the human retina

102

00:06:04,966 --> 00:06:07,400

for looking
at disease progression

103

00:06:07,400 --> 00:06:08,900

and visual impairments

104

00:06:08,900 --> 00:06:11,166

in both terrestrial
human populations

105

00:06:11,166 --> 00:06:13,233

and now astronauts.

106

00:06:13,233 --> 00:06:16,100

These human retinal stories

107

00:06:16,100 --> 00:06:20,266

are supported
by other model systems

108

00:06:20,266 --> 00:06:22,233

in the mouse.

109

00:06:22,233 --> 00:06:26,633
Other systems we have applied
the VESGEN approach to

110
00:06:26,633 --> 00:06:32,366
include gastrointestinal
inflammation...

111
00:06:32,366 --> 00:06:34,566
the venation patterning

112
00:06:34,566 --> 00:06:36,933
in the leaves
of higher land plants,

113
00:06:36,933 --> 00:06:39,533
venation in the wings
of the fruit fly,

114
00:06:39,533 --> 00:06:41,033
Drosophila melanogaster,

115
00:06:41,033 --> 00:06:42,900
which are a very important
genetic model

116
00:06:42,900 --> 00:06:44,666
for drug discovery,

117
00:06:44,666 --> 00:06:48,733
and even, to some extent,
in intra-vital blood flow.

118
00:07:01,300 --> 00:07:04,966
So the story that started
at University of Washington

119
00:07:04,966 --> 00:07:07,933
and continued
when I joined NASA in 2001

120

00:07:07,933 --> 00:07:10,266
is now leading
to our first studies

121

00:07:10,266 --> 00:07:13,000
in the retinas
of the astronauts

122

00:07:13,000 --> 00:07:15,366
pre- and post-flight
to the ISS,

123

00:07:15,366 --> 00:07:18,733
or International Space Station.

124

00:07:18,733 --> 00:07:22,533
NASA has recently identified,
in the past several years,

125

00:07:22,533 --> 00:07:25,333
significant risks
for visual impairments

126

00:07:25,333 --> 00:07:28,300
associated with increased
intracranial pressure

127

00:07:28,300 --> 00:07:32,933
that are associated particularly
with long-duration space flight.

128

00:07:32,933 --> 00:07:34,500
We're just starting
these studies,

129

00:07:34,500 --> 00:07:36,400
and I think we'll have
the results from them

130

00:07:36,400 --> 00:07:40,066

in about a year,
ready for public disclosure,

131

00:07:40,066 --> 00:07:44,466

but it is really the studies
that we did in the avian CAM

132

00:07:44,466 --> 00:07:45,733

and the human retina

133

00:07:45,733 --> 00:07:48,966

that provide the compelling
preliminary evidence

134

00:07:48,966 --> 00:07:51,733

as recognized
by the peer reviewers and NASA

135

00:07:51,733 --> 00:07:54,966

for initiating
these astronaut studies.

136

00:08:01,200 --> 00:08:04,166

We have designed
the VESGEN software

137

00:08:04,166 --> 00:08:08,633

to automatically map and
quantify vascular patterning

138

00:08:08,633 --> 00:08:10,700

from binary images.

139

00:08:10,700 --> 00:08:13,566

According not really
to engineering principles,

140

00:08:13,566 --> 00:08:18,900

but according to physiological
fractal-based-branching rules

141

00:08:18,900 --> 00:08:23,566

that also involve considerations
of anatomy, fluid mechanics,

142

00:08:23,566 --> 00:08:26,300

and cell biology.

143

00:08:26,300 --> 00:08:28,733

These branching rules

that we follow

144

00:08:28,733 --> 00:08:33,500

include vessel bifurcations,
vessel tapering, connectivity,

145

00:08:33,500 --> 00:08:37,866

and also account

for the fluid mechanics

146

00:08:37,866 --> 00:08:40,466

of blood flow.

147

00:08:40,466 --> 00:08:45,900

The three fundamental types

of vascular geometry listed here

148

00:08:45,900 --> 00:08:49,400

include trees

as illustrated by our map--

149

00:08:49,400 --> 00:08:52,400

VESGEN map of the human retina,

150

00:08:52,400 --> 00:08:56,533

vascular networks,

illustrated by the mouse retina,

151
00:08:56,533 --> 00:08:59,266
and then
tree network composites,

152
00:08:59,266 --> 00:09:01,766
of which this really
is an example.

153
00:09:01,766 --> 00:09:04,800
I've again listed here
the various applications

154
00:09:04,800 --> 00:09:09,233
we have tested, published,

155
00:09:09,233 --> 00:09:13,000
and just to say that

156
00:09:13,000 --> 00:09:17,800
the ubiquity of
the fractal-branching phenomenon

157
00:09:17,800 --> 00:09:20,233
has been quite
an interesting story

158
00:09:20,233 --> 00:09:22,200
that I wouldn't have predicted.

159
00:09:25,733 --> 00:09:28,500
This slide illustrates
what I think you all know

160
00:09:28,500 --> 00:09:33,400
is the normal progression
of basic to clinical research

161
00:09:33,400 --> 00:09:36,033
in biomedical studies,

162

00:09:36,033 --> 00:09:39,200

so initially we might identify
and propose

163

00:09:39,200 --> 00:09:42,733

feasibility candidates
for drugs and other therapies

164

00:09:42,733 --> 00:09:47,100

by looking at molecules
and cells in in vitro studies.

165

00:09:47,100 --> 00:09:50,600

After identifying
candidate strategies,

166

00:09:50,600 --> 00:09:54,200

these approaches will be tested

167

00:09:54,200 --> 00:09:58,100

in more complex
in vivo organisms

168

00:09:58,100 --> 00:10:01,300

and ultimately applied
in clinical studies

169

00:10:01,300 --> 00:10:03,566

in human beings.

170

00:10:03,566 --> 00:10:05,333

Now, the CAM model

171

00:10:05,333 --> 00:10:07,966

really represents a model
of intermediate complexity

172

00:10:07,966 --> 00:10:09,766

between cells in a dish

173

00:10:09,766 --> 00:10:13,900
and something like the mouse
or other rodents,

174

00:10:13,900 --> 00:10:15,933
because it's quite
a simple system,

175

00:10:15,933 --> 00:10:19,666
in that you simply have to crack
the egg into a dish,

176

00:10:19,666 --> 00:10:21,000
in this case with quail eggs,

177

00:10:21,000 --> 00:10:23,400
a conventional
six-well culture dish,

178

00:10:23,400 --> 00:10:25,900
and then the little embryo

179

00:10:25,900 --> 00:10:28,933
and its
chorioallantoic membrane

180

00:10:28,933 --> 00:10:32,133
and analog of the human placenta
develop quite quickly

181

00:10:32,133 --> 00:10:34,200
over several days.

182

00:10:38,500 --> 00:10:43,400
You may well ask,
why the quail egg?

183

00:10:43,400 --> 00:10:46,500

And the reason,
as I've just described,

184

00:10:46,500 --> 00:10:50,733

is that it does grow
very quickly.

185

00:10:50,733 --> 00:10:53,133

The chorioallantoic membrane,

186

00:10:53,133 --> 00:10:56,233

which is an out-punching
of the gut,

187

00:10:56,233 --> 00:10:58,466

fills the petri dish

188

00:10:58,466 --> 00:11:01,000

and then is easily dissected
and fixed

189

00:11:01,000 --> 00:11:03,433

as a transparent specimen.

190

00:11:03,433 --> 00:11:05,800

Other conveniences of the model

191

00:11:05,800 --> 00:11:09,100

is that angiogenesis
is very rapid

192

00:11:09,100 --> 00:11:12,233

and is contained
within a 2D vascular tree

193

00:11:12,233 --> 00:11:15,466

that is
microscopically accessible.

194

00:11:20,500 --> 00:11:23,800

The next two slides
demonstrate for you

195

00:11:23,800 --> 00:11:25,566

your own observations--

196

00:11:25,566 --> 00:11:29,200

my initial observations
looking at the system,

197

00:11:29,200 --> 00:11:31,066

in that the application

198

00:11:31,066 --> 00:11:34,133

of the major
angiogenesis regulators

199

00:11:34,133 --> 00:11:38,033

such as FGF2, VEGF,

200

00:11:38,033 --> 00:11:41,300

induced really
the specific fingerprint,

201

00:11:41,300 --> 00:11:45,533

or signature vascular patterns,
you see before you.

202

00:11:45,533 --> 00:11:48,966

My career research really
does focus on angiogenesis,

203

00:11:48,966 --> 00:11:50,700

its stimulation and inhibition

204

00:11:50,700 --> 00:11:54,100

for health
and disease applications.

205

00:11:54,100 --> 00:11:56,066

So what you see compared

206

00:11:56,066 --> 00:11:59,366

after 24 hours

of treatment with FGF

207

00:11:59,366 --> 00:12:03,233

is that it was a simple,

robust stimulator.

208

00:12:03,233 --> 00:12:06,233

It simply induces the growth

209

00:12:06,233 --> 00:12:08,833

of new, small blood vessels

210

00:12:08,833 --> 00:12:11,533

in a dose-dependent fashion.

211

00:12:11,533 --> 00:12:14,900

VEGF, surprisingly,

was more complicated

212

00:12:14,900 --> 00:12:16,266

in its regulation.

213

00:12:16,266 --> 00:12:19,700

At low concentrations, as FGF,

214

00:12:19,700 --> 00:12:22,466

it did stimulate

physiological angiogenesis,

215

00:12:22,466 --> 00:12:25,400

or the growth

of the new small vessels.

216

00:12:25,400 --> 00:12:29,700

However, at larger,
higher concentrations,

217

00:12:29,700 --> 00:12:33,733

there was a phenotypic switch
to a non-angiogenesis pattern

218

00:12:33,733 --> 00:12:36,766

in which the vessels
were dilated, leaky,

219

00:12:36,766 --> 00:12:40,900

and associated
with significant increase

220

00:12:40,900 --> 00:12:45,400

in the activity of endothelial
nitric oxide synthase, or ENOS,

221

00:12:45,400 --> 00:12:48,700

a well-known vessel dilator.

222

00:12:53,000 --> 00:12:58,066

So, when I looked at the major
inhibitors of angiogenesis

223

00:12:58,066 --> 00:13:01,166

that include TGF beta
and angiostatin,

224

00:13:01,166 --> 00:13:03,733

of course,
many other molecules,

225

00:13:03,733 --> 00:13:06,233

again, each of these regulators

226

00:13:06,233 --> 00:13:10,633

induced a distinct
fingerprint pattern of response.

227

00:13:10,633 --> 00:13:13,666
TGF beta, in a sense, like FGF,

228

00:13:13,666 --> 00:13:16,533
targeted the growth
of the new, small vessels

229

00:13:16,533 --> 00:13:18,933
by inhibiting them,

230

00:13:18,933 --> 00:13:23,233
but maintaining the vascular
tree in a normal state.

231

00:13:23,233 --> 00:13:26,000
Angiostatin, on the other hand,

232

00:13:26,000 --> 00:13:29,366
greatly disrupted
normal vascular patterning,

233

00:13:29,366 --> 00:13:33,400
inducing what appeared to be
a pretty pathological phenotype.

234

00:13:38,366 --> 00:13:42,300
So the prevailing hypothesis
in angiogenesis research

235

00:13:42,300 --> 00:13:45,466
was established by
Douglas Hanahan, Judah Folkman,

236

00:13:45,466 --> 00:13:47,433
Noel Bauk, and others,
I would say,

237

00:13:47,433 --> 00:13:49,766

especially during the 1990s,

238

00:13:49,766 --> 00:13:53,233

and still guides research
in the field.

239

00:13:53,233 --> 00:13:58,966

So this hypothesis states
that angiogenesis,

240

00:13:58,966 --> 00:14:01,300

either normal and healthy
in development,

241

00:14:01,300 --> 00:14:05,200

or pathological in diseases
such as cancer and diabetes,

242

00:14:05,200 --> 00:14:08,233

is turned on and off or off

243

00:14:08,233 --> 00:14:10,233

by the net accumulation

244

00:14:10,233 --> 00:14:14,666

of the many stimulators
and inhibitors in our bodies.

245

00:14:17,600 --> 00:14:20,733

Our hypothesis--
the VESGEN hypothesis--

246

00:14:20,733 --> 00:14:24,666

builds on this
angiogenesis hypothesis

247

00:14:24,666 --> 00:14:28,566

by proposing that fingerprint

248

00:14:28,566 --> 00:14:30,600
or signature vascular patterns

249

00:14:30,600 --> 00:14:35,000
really can provide useful,
accessible, integrative readouts

250

00:14:35,000 --> 00:14:37,233
of these very complex,

251

00:14:37,233 --> 00:14:39,466
interacting
molecular signaling pathways

252

00:14:39,466 --> 00:14:40,733
and, of course, even others,

253

00:14:40,733 --> 00:14:44,800
such as hypoxia inducible
growth factor.

254

00:14:44,800 --> 00:14:49,366
To me, this is really the key
slide of the entire talk

255

00:14:49,366 --> 00:14:51,966
because the observations
and measurements

256

00:14:51,966 --> 00:14:53,800
that we made with this system

257

00:14:53,800 --> 00:14:55,933
continue to guide our research

258

00:14:55,933 --> 00:15:00,666
into other organisms
and human disease.

259

00:15:00,666 --> 00:15:05,066

So the basic design principle
of the VESGEN software

260

00:15:05,066 --> 00:15:09,066

is to segment
or dissect the branching tree

261

00:15:09,066 --> 00:15:11,833

into successive
branching generations

262

00:15:11,833 --> 00:15:15,733

so that we can measure where
on the tree or how on the tree

263

00:15:15,733 --> 00:15:18,933

these complex changes
are occurring.

264

00:15:18,933 --> 00:15:20,733

The approach that we take

265

00:15:20,733 --> 00:15:25,000

is that the first-generation
or parent vessel is identified,

266

00:15:25,000 --> 00:15:29,966

and then by fractal and other
physiological principles,

267

00:15:29,966 --> 00:15:32,800

the remaining vessels
are dissected

268

00:15:32,800 --> 00:15:35,366

into their
respective generations.

269

00:15:39,166 --> 00:15:40,900

The reason I think
this is the key slide

270

00:15:40,900 --> 00:15:45,733

is because, as documented
by the complex quantification--

271

00:15:45,733 --> 00:15:49,433

oops, sorry--
in a number of publications,

272

00:15:49,433 --> 00:15:53,400

including
these three publications...

273

00:15:55,566 --> 00:15:58,966

We were able to supply
scientific evidence

274

00:15:58,966 --> 00:16:01,633

in support of this hypothesis.

275

00:16:01,633 --> 00:16:05,933

So, to summarize
by the sketches of the results,

276

00:16:05,933 --> 00:16:10,166

FGF did indeed act, as measured
by our VESGEN results.

277

00:16:10,166 --> 00:16:12,100

as a simple robust stimulator,

278

00:16:12,100 --> 00:16:16,866

in that, with increasing
concentration of the cytokine,

279

00:16:16,866 --> 00:16:19,333

the increasing density

280

00:16:19,333 --> 00:16:24,200

of small, new vessels
were observed.

281

00:16:24,200 --> 00:16:29,000

VEGF--VEGF, as a vascular
complexity factor,

282

00:16:29,000 --> 00:16:33,100

did display these overlapping
patterns of response.

283

00:16:33,100 --> 00:16:36,933

So, at low concentration,
the vessels--

284

00:16:36,933 --> 00:16:39,400

the new, small vessels
did increase

285

00:16:39,400 --> 00:16:44,166

as a physiological
angiogenesis phenomenon.

286

00:16:44,166 --> 00:16:47,233

At higher concentrations,
there was a phenotypic switch

287

00:16:47,233 --> 00:16:51,666

to a pathological
non-angiogenic phenotype

288

00:16:51,666 --> 00:16:55,100

in association
with increased ENOS signaling,

289

00:16:55,100 --> 00:16:57,733

in which there

was increased vessel diameter

290

00:16:57,733 --> 00:17:00,200
and leakage.

291

00:17:00,200 --> 00:17:03,533
TGF beta, as...

292

00:17:03,533 --> 00:17:06,366
something of an inverse
of FGF signaling

293

00:17:06,366 --> 00:17:11,066
with increasing concentration,
did strongly inhibit the growth

294

00:17:11,066 --> 00:17:13,900
of the new, small vessels.

295

00:17:18,633 --> 00:17:22,233
So those results

296

00:17:22,233 --> 00:17:24,133
were mapped
and quantified initially

297

00:17:24,133 --> 00:17:27,533
with the semiautomatic
met lag prototype code

298

00:17:27,533 --> 00:17:30,533
that I wrote while
at University of Washington.

299

00:17:30,533 --> 00:17:33,333
After joining NASA in 2001,

300

00:17:33,333 --> 00:17:36,466
I have to say, it was

my dream and my privilege

301

00:17:36,466 --> 00:17:40,300
to work with a brilliant
computer-science team,

302

00:17:40,300 --> 00:17:42,566
consisting
of a software architect

303

00:17:42,566 --> 00:17:44,900
and an image-processing expert.

304

00:17:44,900 --> 00:17:48,200
So, together, we were able
to fully automate the analysis

305

00:17:48,200 --> 00:17:51,233
into the types of mappings
and quantification

306

00:17:51,233 --> 00:17:53,600
you see illustrated here.

307

00:17:53,600 --> 00:17:55,766
Using, again, however,
our CAM model

308

00:17:55,766 --> 00:17:59,900
as we matured the technology...

309

00:18:01,766 --> 00:18:03,900
With these
cover illustrations, again,

310

00:18:03,900 --> 00:18:08,966
of the CAM branching generations
within the trees.

311

00:18:08,966 --> 00:18:13,066

So, to summarize this more mature phase of our research,

312

00:18:13,066 --> 00:18:16,200

we tested in collaboration with the Cole Eye Institute

313

00:18:16,200 --> 00:18:19,600

the effect of common clinical steroid use in clinics,

314

00:18:19,600 --> 00:18:21,066

not only for the retina,

315

00:18:21,066 --> 00:18:24,333

but for inflammation in other sites, such as the knee.

316

00:18:24,333 --> 00:18:27,100

It's a very well established anti-inflammatory

317

00:18:27,100 --> 00:18:29,866

and anti-angiogenesis drug,

318

00:18:29,866 --> 00:18:33,366

powerful in its inhibitory activities.

319

00:18:33,366 --> 00:18:36,100

So, again, it was no surprise

320

00:18:36,100 --> 00:18:41,366

that we did measure and quantify the significant inhibition

321

00:18:41,366 --> 00:18:45,233

of the small vessels by this drug.

322

00:18:45,233 --> 00:18:48,366

However, because of the
vascular-patterning capabilities

323

00:18:48,366 --> 00:18:50,066

of our analysis,

324

00:18:50,066 --> 00:18:53,466

we did make, I think,
what is a novel discovery--

325

00:18:53,466 --> 00:18:54,733

a useful discovery,

326

00:18:54,733 --> 00:18:59,066

in that the steroid
also thinned the vessels--

327

00:18:59,066 --> 00:19:03,366

the diameters of the vessels
throughout the branching tree.

328

00:19:03,366 --> 00:19:06,200

This effect of the steroid,
we thought,

329

00:19:06,200 --> 00:19:10,800

was related probably to its
primary harmful side effect

330

00:19:10,800 --> 00:19:12,133

in the clinic,

331

00:19:12,133 --> 00:19:16,766

which is associated with
increased risks for glaucoma.

332

00:19:16,766 --> 00:19:21,166

Glaucoma is a condition
whereby the pressure increases

333

00:19:21,166 --> 00:19:23,833

to levels
that it can be blinding,

334

00:19:23,833 --> 00:19:28,233

and so, once we disturbed
the effectiveness

335

00:19:28,233 --> 00:19:32,400

of the vessels
for regulating the fluids

336

00:19:32,400 --> 00:19:35,766

within the eye,
it's possible to imagine

337

00:19:35,766 --> 00:19:39,400

how that could be associated
with glaucoma.

338

00:19:41,566 --> 00:19:43,066

So, finally, to conclude,

339

00:19:43,066 --> 00:19:46,066

the CAM studies description
that we performed,

340

00:19:46,066 --> 00:19:48,066

well, all of us
in research know

341

00:19:48,066 --> 00:19:50,300

there are always the stories
that get away

342

00:19:50,300 --> 00:19:52,766

and you just can't finish

everything.

343

00:19:52,766 --> 00:19:56,166

So I just thought you might
enjoy seeing this slide

344

00:19:56,166 --> 00:19:58,900

in which we tested

345

00:19:58,900 --> 00:20:01,400

an endogenous factor
in our bodies

346

00:20:01,400 --> 00:20:04,566

that surprisingly resulted--

347

00:20:04,566 --> 00:20:06,966

Compared
to the normal control,

348

00:20:06,966 --> 00:20:09,233

it induced the development

349

00:20:09,233 --> 00:20:12,100

of very
highly tortuous vessels--

350

00:20:12,100 --> 00:20:14,600

these little
corkscrew vessels here.

351

00:20:14,600 --> 00:20:17,333

And, of course,
that also has implications

352

00:20:17,333 --> 00:20:19,733

for disease and health.

353

00:20:23,266 --> 00:20:26,500

Well, after seeing a number
of slides of our CAM studies

354

00:20:26,500 --> 00:20:31,200

as our initial biological
and engineering testbed model

355

00:20:31,200 --> 00:20:33,133

for developing the technology,

356

00:20:33,133 --> 00:20:36,566

I think you probably
can all recognize in this slide

357

00:20:36,566 --> 00:20:40,066

the similarity
of the branching trees

358

00:20:40,066 --> 00:20:42,566

and our own human retinas

359

00:20:42,566 --> 00:20:45,600

with the vascular patterns
in the CAM.

360

00:20:45,600 --> 00:20:48,200

The CAM is often used
in research

361

00:20:48,200 --> 00:20:51,633

as a morphological analog
of the retina,

362

00:20:51,633 --> 00:20:53,900

and, indeed,
it was a former director

363

00:20:53,900 --> 00:20:57,133

of the United States
National Eye Institute

364
00:20:57,133 --> 00:21:01,900
who suggested to us
when I was in Washington

365
00:21:01,900 --> 00:21:03,833
that we use
our CAM VESGEN analysis

366
00:21:03,833 --> 00:21:07,166
for looking
at human retinal disease.

367
00:21:07,166 --> 00:21:09,966
So these studies
actually were done

368
00:21:09,966 --> 00:21:11,900
at the University of Washington

369
00:21:11,900 --> 00:21:14,200
with the Department
of Ophthalmology,

370
00:21:14,200 --> 00:21:16,400
and here what we did

371
00:21:16,400 --> 00:21:19,900
was to take
our CAM methodology,

372
00:21:19,900 --> 00:21:22,233
which was to...

373
00:21:24,400 --> 00:21:26,633
Assign the various portions
of the retina

374
00:21:26,633 --> 00:21:28,600

according
to the regions identified

375
00:21:28,600 --> 00:21:30,500
by the ophthalmologists

376
00:21:30,500 --> 00:21:32,933
and then use
the fractal analysis

377
00:21:32,933 --> 00:21:35,233
to measure
and compare these regions

378
00:21:35,233 --> 00:21:38,433
of healthy human retinas

379
00:21:38,433 --> 00:21:42,333
with early-stage disease
and diabetic retinopathy.

380
00:21:42,333 --> 00:21:45,333
Diabetic retinopathy
is the major blind disease

381
00:21:45,333 --> 00:21:47,433
for working-aged adults.

382
00:21:47,433 --> 00:21:49,900
So, taking these approaches,

383
00:21:49,900 --> 00:21:53,933
we did see that indeed
there was strong vessel dropout

384
00:21:53,933 --> 00:21:56,766
in the central region
of the retina, the macula,

385

00:21:56,766 --> 00:22:00,733
which is very important
for human and primate vision.

386
00:22:02,566 --> 00:22:05,766
And this slide actually
was shown a few years later

387
00:22:05,766 --> 00:22:10,200
at the annual International
Ophthalmology Research Meeting,

388
00:22:10,200 --> 00:22:13,866
and since then,
a number of institutes

389
00:22:13,866 --> 00:22:15,566
in Australia and Singapore,

390
00:22:15,566 --> 00:22:18,966
where vision research
is very important

391
00:22:18,966 --> 00:22:23,033
because of the challenges
to vision in the tropics,

392
00:22:23,033 --> 00:22:24,800
have established
the fractal dimension

393
00:22:24,800 --> 00:22:28,300
as one of their ways
of measuring vascular change

394
00:22:28,300 --> 00:22:30,733
with the progression
of disease.

395
00:22:33,833 --> 00:22:36,266

Since the title of our talk is

396

00:22:36,266 --> 00:22:40,200

"Fractal-Based Analysis
of Vascular Remodeling,"

397

00:22:40,200 --> 00:22:41,766

I thought I should
spend a little time

398

00:22:41,766 --> 00:22:45,333

talking about fractal methods.

399

00:22:45,333 --> 00:22:48,866

So fractal mathematics
was developed by Mandelbrot

400

00:22:48,866 --> 00:22:51,366

and others in the 1980s,

401

00:22:51,366 --> 00:22:54,566

and it's a non-Euclidean way

402

00:22:54,566 --> 00:22:58,633

of looking at many complex,
space-filling structures

403

00:22:58,633 --> 00:23:03,666

in nature,
such as lightning, trees,

404

00:23:03,666 --> 00:23:05,900

coastline topography,

405

00:23:05,900 --> 00:23:08,733

vascular
and neuronal branching.

406

00:23:10,633 --> 00:23:12,566

And I think some of you
in the audience

407
00:23:12,566 --> 00:23:15,000
who focus more
in the nervous system

408
00:23:15,000 --> 00:23:19,200
will pretty quickly see
the similarity of branching

409
00:23:19,200 --> 00:23:21,433
in this lightning

410
00:23:21,433 --> 00:23:24,833
with neuronal branching
in our bodies.

411
00:23:24,833 --> 00:23:28,166
A fundamental concept
of fractal mathematics,

412
00:23:28,166 --> 00:23:31,833
probably the key one
for branching structures,

413
00:23:31,833 --> 00:23:34,966
is the idea of self-similarity.

414
00:23:34,966 --> 00:23:39,466
So this is the phenomenon--
the fractal phenomenon

415
00:23:39,466 --> 00:23:42,033
whereby larger
branching structures,

416
00:23:42,033 --> 00:23:45,166
such as you see up here,

417
00:23:45,166 --> 00:23:48,366
successively iterate
that branching pattern

418
00:23:48,366 --> 00:23:51,100
at smaller-
and smaller-length scales.

419
00:23:51,100 --> 00:23:52,733
So you will see down here

420
00:23:52,733 --> 00:23:55,066
another branching event

421
00:23:55,066 --> 00:23:56,833
that becomes smaller
and smaller,

422
00:23:56,833 --> 00:24:00,566
but essentially repeats
the branching structure.

423
00:24:10,966 --> 00:24:14,800
So, just to say again, that
the pattern in the lightning

424
00:24:14,800 --> 00:24:17,200
is really rather different
from vascular branching,

425
00:24:17,200 --> 00:24:18,966
which is water-based,

426
00:24:18,966 --> 00:24:21,433
but the patterns when people
ask us to use VESGEN

427
00:24:21,433 --> 00:24:22,933
for neuronal branching

428

00:24:22,933 --> 00:24:24,266
are really somewhat different,

429

00:24:24,266 --> 00:24:27,866
and I think have some kind
of eerie connection

430

00:24:27,866 --> 00:24:29,633
with the branching
in the lightning

431

00:24:29,633 --> 00:24:34,533
because our neurons connect
by electrical signaling.

432

00:24:37,100 --> 00:24:40,733
So, looking
at fractal algorithms

433

00:24:40,733 --> 00:24:45,066
in the late '90s
when I started this research,

434

00:24:45,066 --> 00:24:47,600
I identified
the box-counting algorithm

435

00:24:47,600 --> 00:24:51,133
as the most reproducible
and sensitive

436

00:24:51,133 --> 00:24:53,900
for detection
of branching patterns

437

00:24:53,900 --> 00:24:56,833
in vascular structures.

438

00:24:56,833 --> 00:24:58,733

So this--

439

00:24:58,733 --> 00:25:01,100

You see here,

from this vascular structure,

440

00:25:01,100 --> 00:25:03,900

that the box counting yields

a fractal dimension

441

00:25:03,900 --> 00:25:06,233

of 1.41.

442

00:25:09,566 --> 00:25:13,866

So, as defined by Mandelbrot

and the other mathematicians

443

00:25:13,866 --> 00:25:16,966

creating this new mathematics,

444

00:25:16,966 --> 00:25:21,233

in a 2D binary,

445

00:25:21,233 --> 00:25:23,333

black-white vascular image,

446

00:25:23,333 --> 00:25:26,866

the fractal dimension

of a branching structure,

447

00:25:26,866 --> 00:25:29,433

such as the vasculature,

448

00:25:29,433 --> 00:25:31,066

must necessarily lie

449

00:25:31,066 --> 00:25:33,666

between the dimension

of a line--

450

00:25:33,666 --> 00:25:35,666

one dimension
and two dimensions,

451

00:25:35,666 --> 00:25:38,266

such as in a square
or a rectangle.

452

00:25:38,266 --> 00:25:41,833

So, in this case, as we
discussed in the previous slide,

453

00:25:41,833 --> 00:25:45,866

the fractal dimension will
always be a fractional quantity

454

00:25:45,866 --> 00:25:48,233

defined by those limits.

455

00:25:50,133 --> 00:25:54,300

So, now, after having examined
the concept

456

00:25:54,300 --> 00:25:58,900

of self-similar branching
in the lightning photograph,

457

00:25:58,900 --> 00:26:01,633

I think you can now see
how this concept

458

00:26:01,633 --> 00:26:06,200

of self-similar branching

459

00:26:06,200 --> 00:26:09,600

is repeated through about
eight generations of branching

460
00:26:09,600 --> 00:26:11,900
in the CAM specimen.

461
00:26:11,900 --> 00:26:14,200
Just to say
that mathematical fractals,

462
00:26:14,200 --> 00:26:17,933
such as the Julia set,
the Koch curve,

463
00:26:17,933 --> 00:26:21,400
those kinds
of mathematical fractals

464
00:26:21,400 --> 00:26:22,933
can iterate themselves

465
00:26:22,933 --> 00:26:24,733
through infinite numbers
of generations,

466
00:26:24,733 --> 00:26:27,700
but in nature,
such as the vascular system,

467
00:26:27,700 --> 00:26:31,366
the self-similar patterns

468
00:26:31,366 --> 00:26:35,300
will typically repeat themselves
up to generations of about--

469
00:26:35,300 --> 00:26:38,133
or iterations
of about eight to ten.

470
00:26:41,400 --> 00:26:44,733
So, as I described in the CAM,

471

00:26:44,733 --> 00:26:47,800

looking
at normal healthy development,

472

00:26:47,800 --> 00:26:50,100

which, of course,
is a very important aspect

473

00:26:50,100 --> 00:26:53,066

of this kind of phenomenon,

474

00:26:53,066 --> 00:26:58,566

the fractal branching patterns
quickly fill themselves in

475

00:26:58,566 --> 00:27:00,333

over about five days,

476

00:27:00,333 --> 00:27:05,166

six days
of vascular development.

477

00:27:05,166 --> 00:27:08,600

And one result that continues
to fascinate me

478

00:27:08,600 --> 00:27:11,233

from that early research
is the fact that

479

00:27:11,233 --> 00:27:15,600

that fractal-based
growth pattern

480

00:27:15,600 --> 00:27:17,133

becomes a linear result

481

00:27:17,133 --> 00:27:22,666

when analyzed
by fractal mathematics.

482
00:27:22,666 --> 00:27:26,900
So you see here that
that growth pattern

483
00:27:26,900 --> 00:27:29,566
of the vessels is indeed linear

484
00:27:29,566 --> 00:27:33,133
during
that developmental window,

485
00:27:33,133 --> 00:27:35,666
and this really
is an exponential phenomenon,

486
00:27:35,666 --> 00:27:37,066
analogous to talks we heard

487
00:27:37,066 --> 00:27:39,566
in our own space biology
last week,

488
00:27:39,566 --> 00:27:43,600
in which the growth rates
of microbes and cells

489
00:27:43,600 --> 00:27:49,066
also display
a linear pattern of growth

490
00:27:49,066 --> 00:27:51,366
because they are dependent--

491
00:27:51,366 --> 00:27:52,900
the rate of change is dependent

492

00:27:52,900 --> 00:27:56,066
on the current state
of the system.

493
00:27:58,900 --> 00:28:03,300
So, to summarize
at this portion of the talk,

494
00:28:03,300 --> 00:28:07,033
just want to say that we have
accumulated evidence

495
00:28:07,033 --> 00:28:11,233
in a number of systems
about the fact

496
00:28:11,233 --> 00:28:14,000
that fingerprint
or signature vascular patterns

497
00:28:14,000 --> 00:28:17,300
may offer biologists
and physicians

498
00:28:17,300 --> 00:28:19,633
useful, accessible readouts

499
00:28:19,633 --> 00:28:23,400
of dominant molecular
regulators and pathways.

500
00:28:26,066 --> 00:28:27,800
The system is fractal-based,

501
00:28:27,800 --> 00:28:29,900
but in order
to really describe it,

502
00:28:29,900 --> 00:28:32,100
we need a number

of other repertoires,

503

00:28:32,100 --> 00:28:33,933

a suite of repertoires,

504

00:28:33,933 --> 00:28:36,633

because at least in the current
state of fractal analysis,

505

00:28:36,633 --> 00:28:41,733

which is an early, early stage
in its development,

506

00:28:41,733 --> 00:28:44,700

really, you can have
the same fractal dimension

507

00:28:44,700 --> 00:28:47,233

for quite different
vascular patterns.

508

00:28:47,233 --> 00:28:49,233

The dimension may describe

509

00:28:49,233 --> 00:28:51,033

the space-filling
characteristics,

510

00:28:51,033 --> 00:28:53,666

but the patterns are not--

511

00:28:53,666 --> 00:28:56,000

don't have to be the same.

512

00:28:56,000 --> 00:28:58,500

So it's really
a nonunique descriptor.

513

00:28:58,500 --> 00:29:01,900

Therefore, to quantify changes

514

00:29:01,900 --> 00:29:04,966
in a sight-specific manner
within the tree,

515

00:29:04,966 --> 00:29:07,666
we have other parameters,
such as number density,

516

00:29:07,666 --> 00:29:10,566
length density,
and branch points.

517

00:29:13,433 --> 00:29:16,933
So, in collaboration
with Dr. Peter Kaiser,

518

00:29:16,933 --> 00:29:20,466
vitreoretinal surgeon
at the Cole Eye institute,

519

00:29:20,466 --> 00:29:23,733
we did embark
upon a new NIH study

520

00:29:23,733 --> 00:29:25,933
after I joined NASA.

521

00:29:25,933 --> 00:29:28,933
And so you see illustrated here

522

00:29:28,933 --> 00:29:32,633
the progression
of this blinding disease,

523

00:29:32,633 --> 00:29:35,266
from a normal, healthy retina

524

00:29:35,266 --> 00:29:38,233
to early stages
and the late, binding stages

525
00:29:38,233 --> 00:29:39,866
when the vessels
have overgrown,

526
00:29:39,866 --> 00:29:44,066
and the neovascularization
is blinding

527
00:29:44,066 --> 00:29:46,566
and very abnormal.

528
00:29:50,300 --> 00:29:53,300
So, applying the methods
and technology

529
00:29:53,300 --> 00:29:56,166
that we developed in the CAM
to the human retina

530
00:29:56,166 --> 00:29:58,333
and the progression
of this disease,

531
00:29:58,333 --> 00:30:01,800
you can see the maps
of the arterial trees

532
00:30:01,800 --> 00:30:06,566
through mild, moderate, severe,
and very late-blinding stage,

533
00:30:06,566 --> 00:30:10,833
as well as in the venous trees.

534
00:30:12,766 --> 00:30:14,533
So we were surprised

to discover

535

00:30:14,533 --> 00:30:17,800

that there was actually
a very strong regeneration

536

00:30:17,800 --> 00:30:21,266

of the small vessels as measured
by the VESGEN analysis

537

00:30:21,266 --> 00:30:23,600

at an early stage
of the disease,

538

00:30:23,600 --> 00:30:27,066

because the prevailing paradigm
for some decades

539

00:30:27,066 --> 00:30:30,466

has been that the vessels
simply drop out in early stages

540

00:30:30,466 --> 00:30:34,400

and then regrow abnormally
at the late stage.

541

00:30:34,400 --> 00:30:37,333

So this discovery
of the regeneration

542

00:30:37,333 --> 00:30:40,566

of more normal vessels
at an early stage

543

00:30:40,566 --> 00:30:41,833

interests, for example,

544

00:30:41,833 --> 00:30:44,733

our new NIH study
with an endocrinologist

545

00:30:44,733 --> 00:30:48,733

working in the diabetic kidney
and retina,

546

00:30:48,733 --> 00:30:51,733

because she is globally renowned

547

00:30:51,733 --> 00:30:53,900

in adult stem-cell therapy.

548

00:30:53,900 --> 00:30:56,766

So why she wants
to work with us

549

00:30:56,766 --> 00:31:00,566

is because, hopefully,
these results

550

00:31:00,566 --> 00:31:02,566

will help her develop

551

00:31:02,566 --> 00:31:06,766

and fine-tune
adult stem-cell repair

552

00:31:06,766 --> 00:31:08,866

of the retina at early stages

553

00:31:08,866 --> 00:31:10,633

before these
late-blinding stages

554

00:31:10,633 --> 00:31:14,233

when there really isn't too much
you can do to repair the retina.

555

00:31:17,400 --> 00:31:20,366

Well, just to say, too,

these preliminary results

556

00:31:20,366 --> 00:31:23,700

led to our NASA funding,

557

00:31:23,700 --> 00:31:26,400

because, again,

with the astronauts,

558

00:31:26,400 --> 00:31:30,066

if only about 50% of the

astronauts incur these damages

559

00:31:30,066 --> 00:31:33,333

after long-duration

space flight,

560

00:31:33,333 --> 00:31:35,366

this kind of analysis

may provide

561

00:31:35,366 --> 00:31:37,900

more early-stage identification

562

00:31:37,900 --> 00:31:40,166

of the early vascular changes

563

00:31:40,166 --> 00:31:44,166

that must necessarily precede

the later damages to the retina,

564

00:31:44,166 --> 00:31:48,200

such as visual impairment

and cotton wool spots.

565

00:31:50,900 --> 00:31:54,666

However, the imaging technology

in ophthalmology

566

00:31:54,666 --> 00:31:58,200
is rapidly evolving,
and, really, the key companies

567
00:31:58,200 --> 00:32:02,066
initiating this reside
in our very own Silicon Valley,

568
00:32:02,066 --> 00:32:04,766
like Zeiss, Heidelberg,
OptiView.

569
00:32:04,766 --> 00:32:07,200
So, for the first time
in the human retina,

570
00:32:07,200 --> 00:32:09,500
because of its
optical accessibility

571
00:32:09,500 --> 00:32:12,333
through the transparency
of our vitreous,

572
00:32:12,333 --> 00:32:15,400
all the vessels
are being visualized,

573
00:32:15,400 --> 00:32:19,166
and this is really a revolution
in clinical ophthalmology

574
00:32:19,166 --> 00:32:22,566
that's happening over
the next year as we speak.

575
00:32:22,566 --> 00:32:25,866
So, working with Richard Rosen
and others

576

00:32:25,866 --> 00:32:28,833
at the New York Eye and Ear
Infirmary Institute,

577
00:32:28,833 --> 00:32:32,433
we're beginning to use
the VESGEN

578
00:32:32,433 --> 00:32:36,233
for these kinds
of new imaging technologies,

579
00:32:36,233 --> 00:32:38,566
and what you can see--

580
00:32:38,566 --> 00:32:40,866
when we do have
the quantification--

581
00:32:40,866 --> 00:32:43,266
I'm sorry. I can only
really provide the maps

582
00:32:43,266 --> 00:32:44,800
in the scope of this talk.

583
00:32:44,800 --> 00:32:47,233
But central retinal
vein occlusion

584
00:32:47,233 --> 00:32:50,533
is a common retinal visual
impairing disorder.

585
00:32:50,533 --> 00:32:53,933
So we were able
to map the vessels

586
00:32:53,933 --> 00:32:56,933
and compare them

with a normal, healthy control

587

00:32:56,933 --> 00:32:59,600

where you see the avascular area
of the macula--

588

00:32:59,600 --> 00:33:02,833

again, very important
for human and primate vision--

589

00:33:02,833 --> 00:33:05,533

compared to the loss
of vessels in CRVO

590

00:33:05,533 --> 00:33:08,100

and an intermediate state
in the fellow eye

591

00:33:08,100 --> 00:33:10,900

of this particular patient.

592

00:33:10,900 --> 00:33:13,033

And I do want to comment
at this point

593

00:33:13,033 --> 00:33:16,966

that as I attend these annual
ophthalmology research meetings

594

00:33:16,966 --> 00:33:18,700

over the last ten years,

595

00:33:18,700 --> 00:33:22,333

I have to say that NASA...

596

00:33:22,333 --> 00:33:25,133

optical and imaging evolutions

597

00:33:25,133 --> 00:33:27,900

for telescopes and astronomy

598

00:33:27,900 --> 00:33:29,900

are frequently cited
as contributing

599

00:33:29,900 --> 00:33:33,566

to the evolutions
in this biomedical imaging,

600

00:33:33,566 --> 00:33:35,266

including
this particular technique--

601

00:33:35,266 --> 00:33:39,900

the adaptive optics technique
that we studied here.

602

00:33:42,533 --> 00:33:45,400

So, as I've described,
we're starting to embark

603

00:33:45,400 --> 00:33:49,033

upon looking at the astronauts
pre and postflight,

604

00:33:49,033 --> 00:33:51,866

and I can't even predict
how that's going to end up

605

00:33:51,866 --> 00:33:53,900

a year from now
because of bringing in

606

00:33:53,900 --> 00:33:55,933

these new imaging technologies

607

00:33:55,933 --> 00:34:00,566

that show for the first time
all the small vessels.

608

00:34:00,566 --> 00:34:03,133

So now, in the remaining period
of the talk,

609

00:34:03,133 --> 00:34:04,900

I would like
to introduce you quickly--

610

00:34:04,900 --> 00:34:07,800

just an overview--pictures
are worth a thousand words--

611

00:34:07,800 --> 00:34:10,466

of some of the other tissue
and organism

612

00:34:10,466 --> 00:34:12,933

and disease applications.

613

00:34:12,933 --> 00:34:16,966

So we've had
about 145 requests worldwide

614

00:34:16,966 --> 00:34:19,533

from every continent
except Antarctica,

615

00:34:19,533 --> 00:34:23,400

institutions
such as Harvard, Mayo Clinic,

616

00:34:23,400 --> 00:34:26,066

the U.S. Environmental
Protection Agency

617

00:34:26,066 --> 00:34:27,666

for toxicology studies,

618

00:34:27,666 --> 00:34:31,100

where the biomedical
researchers working

619

00:34:31,100 --> 00:34:34,000

in head-to-toe
vascular-dependent applications,

620

00:34:34,000 --> 00:34:37,500

such as cancer, diabetes,
heart disease,

621

00:34:37,500 --> 00:34:39,500

would like to be able
to use our software,

622

00:34:39,500 --> 00:34:42,500

and this, for me, was a big
motivation in coming to Ames

623

00:34:42,500 --> 00:34:46,000

because of the life-sciences
expertise at Ames.

624

00:34:46,000 --> 00:34:48,666

Ames is the home
of the space biology--

625

00:34:48,666 --> 00:34:50,566

leads the space biology
for NASA.

626

00:34:50,566 --> 00:34:55,400

And also, the IT supercomputing
expertise here.

627

00:34:58,033 --> 00:34:59,900

So...

628

00:35:01,566 --> 00:35:05,100

Dr. Reinecker, who is
an oncologist/immunologist

629

00:35:05,100 --> 00:35:06,300
at Harvard

630

00:35:06,300 --> 00:35:09,300
studies GI inflammation
and its regulation

631

00:35:09,300 --> 00:35:11,800
with really superb
intravital imaging.

632

00:35:11,800 --> 00:35:13,600
So he sent us these images,

633

00:35:13,600 --> 00:35:16,866
and we have analyzed this

634

00:35:16,866 --> 00:35:20,300
with the network option
of the VESGEN,

635

00:35:20,300 --> 00:35:23,300
in which you can see clearly
the increasing inflammation

636

00:35:23,300 --> 00:35:27,766
and, really, the increasing
irregularity and disorder

637

00:35:27,766 --> 00:35:32,666
of our normally
very regular vascular networks.

638

00:35:35,266 --> 00:35:37,766
Similar studies
of network tree composites

639

00:35:37,766 --> 00:35:41,200
were done with John Sears
in a model of infant retinopathy

640

00:35:41,200 --> 00:35:46,066
of prematurity
at the Cole Eye Institute

641

00:35:46,066 --> 00:35:48,633
and with Michiko Watanabe
and others

642

00:35:48,633 --> 00:35:51,366
at University Hospitals
and Case Western.

643

00:35:51,366 --> 00:35:54,700
We used the VESGEN network--

644

00:35:54,700 --> 00:36:00,433
tree network
and tree analysis options

645

00:36:00,433 --> 00:36:02,700
to chart the development
of the coronary vessels

646

00:36:02,700 --> 00:36:06,333
from their initial very diffuse,
amorphous network

647

00:36:06,333 --> 00:36:08,733
into transitional structures

648

00:36:08,733 --> 00:36:12,200
and ultimately
a mature, tapering vascular tree

649

00:36:12,200 --> 00:36:14,566

around the little mouse heart.

650

00:36:16,066 --> 00:36:18,400

Working now here
in space biology

651

00:36:18,400 --> 00:36:22,900

with Sharmila Bhattacharya
and Ravikumar Hosamani,

652

00:36:22,900 --> 00:36:26,500

we're starting to look at
venation in the fruit-fly wing,

653

00:36:26,500 --> 00:36:29,433

which is a major genetic model.

654

00:36:29,433 --> 00:36:31,566

What's very interesting
about this system--

655

00:36:31,566 --> 00:36:34,000

Of course, it's a major model
for the ISS

656

00:36:34,000 --> 00:36:36,566

and space biology exploration,

657

00:36:36,566 --> 00:36:38,466

but what I find fascinating
in this area

658

00:36:38,466 --> 00:36:41,766

is that the insect wing
is very stereotyped

659

00:36:41,766 --> 00:36:43,700

in its vascular patterning,

660

00:36:43,700 --> 00:36:45,933
so every fruit fly
has essentially

661
00:36:45,933 --> 00:36:48,166
the same vascular pattern.

662
00:36:48,166 --> 00:36:51,300
This is fundamentally different
from vertebrate biology,

663
00:36:51,300 --> 00:36:54,600
in which each CAM was
as unique as a fingerprint.

664
00:36:54,600 --> 00:36:58,166
Similarly
for our own human retina,

665
00:36:58,166 --> 00:36:59,733
each of your vascular patterns

666
00:36:59,733 --> 00:37:02,166
will be as unique
as your fingerprint,

667
00:37:02,166 --> 00:37:04,900
and yet,
the space-filling capacity

668
00:37:04,900 --> 00:37:07,733
of these CAM
and retinal structures

669
00:37:07,733 --> 00:37:09,000
are very uniform

670
00:37:09,000 --> 00:37:12,200
when measured
by a fractal-based analysis,

671

00:37:12,200 --> 00:37:14,633
driven undoubtedly
by uniform needs

672

00:37:14,633 --> 00:37:18,233
within the tissue for oxygen.

673

00:37:18,233 --> 00:37:20,900
So...

674

00:37:20,900 --> 00:37:24,566
now to talk a little bit
about blood flow.

675

00:37:24,566 --> 00:37:27,066
Mark Burnett is a scientist

676

00:37:27,066 --> 00:37:29,666
working in aerodynamics at NASA,

677

00:37:29,666 --> 00:37:33,933
who developed a particle-imaging
velocimetry code,

678

00:37:33,933 --> 00:37:35,566
his PIV prog,

679

00:37:35,566 --> 00:37:39,633
to chart the flow of particles

680

00:37:39,633 --> 00:37:42,500
within the large wind tunnels
we see about us at NASA,

681

00:37:42,500 --> 00:37:45,833
flowing at Mach speeds
of 1, 2, 3.

682

00:37:45,833 --> 00:37:50,066

So we used his software...

683

00:37:50,066 --> 00:37:52,566

in the quail embryo,

684

00:37:52,566 --> 00:37:56,266

in this case the yolk sack
vessels, not the CAM,

685

00:37:56,266 --> 00:38:00,600

to look at blood flow
intravitaly.

686

00:38:00,600 --> 00:38:02,500

So I think you can see
in this movie,

687

00:38:02,500 --> 00:38:05,466

the physiological fact that--

688

00:38:05,466 --> 00:38:07,400

If I can get it up there--

689

00:38:09,733 --> 00:38:12,966

The red blood cells,
which are the particle markers,

690

00:38:12,966 --> 00:38:15,400

are flowing much more slowly
in the small vessels

691

00:38:15,400 --> 00:38:18,666

before being collected
into the much faster flow

692

00:38:18,666 --> 00:38:21,400

of the larger collecting vein.

693

00:38:23,533 --> 00:38:27,233

So, when measured
by his PIV software

694

00:38:27,233 --> 00:38:30,200

that worked at Mach speeds of
1, 2, and 3 in the wind tunnels,

695

00:38:30,200 --> 00:38:35,066

we were able successfully
to track the velocity profiles--

696

00:38:35,066 --> 00:38:37,233

the overall
volumetric flow rates--

697

00:38:37,233 --> 00:38:41,433

of the blood flow in these
little microscopic vessels,

698

00:38:41,433 --> 00:38:45,400

and even to the degree

699

00:38:45,400 --> 00:38:46,900

of resolving the effect

700

00:38:46,900 --> 00:38:49,200

of the pulsatility
of the beating heart

701

00:38:49,200 --> 00:38:51,033

upon the rate
of the blood flow.

702

00:38:51,033 --> 00:38:53,800

Of course, it required not only
his PIV prog software

703

00:38:53,800 --> 00:38:56,800

but also his high-speed
photonics camera

704

00:38:56,800 --> 00:38:59,033
to accomplish this study.

705

00:38:59,033 --> 00:39:01,266
And then we've used
the VESGEN now

706

00:39:01,266 --> 00:39:03,833
to start looking
at "Arabidopsis thaliana,"

707

00:39:03,833 --> 00:39:06,500
a very important space biology
and terrestrial model

708

00:39:06,500 --> 00:39:08,400
for plants,

709

00:39:08,400 --> 00:39:12,633
and, again, it's a fascinating
fractal rescaling story,

710

00:39:12,633 --> 00:39:14,500
as in all of these tissues,

711

00:39:14,500 --> 00:39:17,366
because this down here
is the actual size

712

00:39:17,366 --> 00:39:20,300
of the vascularized plant,
which after--

713

00:39:20,300 --> 00:39:23,166
within six days has grown
to this much more complete

714

00:39:23,166 --> 00:39:26,966
and yet ever fractally branching
and growing structure.

715

00:39:31,400 --> 00:39:32,566
My final training was

716

00:39:32,566 --> 00:39:34,533
at University of California,
San Francisco,

717

00:39:34,533 --> 00:39:37,033
in the laboratory
of Donald McDonald,

718

00:39:37,033 --> 00:39:40,833
who is globally recognized
for his abilities

719

00:39:40,833 --> 00:39:45,300
to visualize vessels in tumors
and inflammatory disease.

720

00:39:45,300 --> 00:39:49,300
So many of the techniques
I've developed since then

721

00:39:49,300 --> 00:39:52,533
in my own research
were learned in his laboratory,

722

00:39:52,533 --> 00:39:55,866
working on re-expression
of, in this case,

723

00:39:55,866 --> 00:39:58,300
the alpha phi beta one integrin

724

00:39:58,300 --> 00:40:01,566

that increases
with increasing tumor size.

725
00:40:03,366 --> 00:40:05,466
So, for those of us
working in biology,

726
00:40:05,466 --> 00:40:07,900
an interesting phenomenon
in the field

727
00:40:07,900 --> 00:40:11,333
is that you talk
about molecular mechanism,

728
00:40:11,333 --> 00:40:15,300
morphological mechanisms,
blood flow,

729
00:40:15,300 --> 00:40:17,433
even cell-biology mechanisms

730
00:40:17,433 --> 00:40:20,533
and these are all perspectives

731
00:40:20,533 --> 00:40:23,800
on a very complex,
interdependent system

732
00:40:23,800 --> 00:40:26,000
that is a living organism.

733
00:40:26,000 --> 00:40:28,033
So there's no time
to talk about this today,

734
00:40:28,033 --> 00:40:29,333
but I just wanted to show you,

735

00:40:29,333 --> 00:40:32,100
as my news-based
biology colleagues,

736
00:40:32,100 --> 00:40:36,400
that we really can, using
the imaging technology--

737
00:40:36,400 --> 00:40:38,900
modern imaging technology
in which you can visualize

738
00:40:38,900 --> 00:40:40,966
the expression
of a single molecule--

739
00:40:40,966 --> 00:40:45,566
a single gene or protein
via fluorescence microscopy

740
00:40:45,566 --> 00:40:48,000
that this really provides a link

741
00:40:48,000 --> 00:40:52,333
between the VESGEN
vascular analysis

742
00:40:52,333 --> 00:40:56,166
and the very complex...

743
00:40:56,166 --> 00:40:59,066
expression profiles
of genomics,

744
00:40:59,066 --> 00:41:01,433
proteomics, metabolomics,

745
00:41:01,433 --> 00:41:03,866
the other kinds
of omics technology

746

00:41:03,866 --> 00:41:07,400
that are being now investigated

747

00:41:07,400 --> 00:41:09,833
by our new gene lab.

748

00:41:09,833 --> 00:41:12,000
So what we are now doing
with the plant leaves

749

00:41:12,000 --> 00:41:14,233
and in other studies
are thinking

750

00:41:14,233 --> 00:41:17,066
about incorporating
essentially endless number

751

00:41:17,066 --> 00:41:21,600
of biomedic bioinformatic
dimensions of information,

752

00:41:21,600 --> 00:41:24,733
along with the Euclidean
branching patterns

753

00:41:24,733 --> 00:41:27,566
of the vascular morphology...

754

00:41:29,133 --> 00:41:31,966
Some of
the cell-biology mechanisms

755

00:41:31,966 --> 00:41:34,433
of the lymphatic system,
in this case,

756

00:41:34,433 --> 00:41:36,900

and the associated
smooth muscle

757

00:41:36,900 --> 00:41:41,233

that covers
the nearby vessels.

758

00:41:41,233 --> 00:41:43,566

We did summarize these studies
with our model

759

00:41:43,566 --> 00:41:45,800

of several
cell-biology mechanisms

760

00:41:45,800 --> 00:41:49,900

participating in various phases
in angiogenesis.

761

00:41:49,900 --> 00:41:53,266

So I don't think I have time to
demonstrate the software today,

762

00:41:53,266 --> 00:41:56,400

but we'd be very happy to show
it to anyone who's interested.

763

00:41:56,400 --> 00:41:58,466

We've got it uploaded
on the software.

764

00:41:58,466 --> 00:42:02,200

Basically, it presents
to the biomedical researcher

765

00:42:02,200 --> 00:42:04,966

the three options
of a vascular tree network

766

00:42:04,966 --> 00:42:06,900

or tree network composite

767

00:42:06,900 --> 00:42:09,266
and then maps
and then quantifies,

768

00:42:09,266 --> 00:42:11,600
along with your
calibration factor,

769

00:42:11,600 --> 00:42:13,866
these various types of images.

770

00:42:15,600 --> 00:42:17,900
So I think what I've tried
to introduce today

771

00:42:17,900 --> 00:42:22,333
is the ubiquity of complex,
fractal-based vascular systems

772

00:42:22,333 --> 00:42:27,233
for higher organisms on Earth,
including humans.

773

00:42:27,233 --> 00:42:30,366
The vascular branching
is fractal-based

774

00:42:30,366 --> 00:42:34,666
and, I think, offers us a system
that necessarily integrates

775

00:42:34,666 --> 00:42:38,900
very complex molecular
and pathway signaling.

776

00:42:40,900 --> 00:42:42,466
Using this research tool,

777

00:42:42,466 --> 00:42:44,200

we've made some
surprising discoveries.

778

00:42:44,200 --> 00:42:46,200

Most often we merely confirm

779

00:42:46,200 --> 00:42:48,400

what you might
plausibly hypothesize

780

00:42:48,400 --> 00:42:50,200

or what is already known,

781

00:42:50,200 --> 00:42:52,300

but then, now and then,
there are the surprises

782

00:42:52,300 --> 00:42:57,066

that indicate important
new avenues of research.

783

00:42:57,066 --> 00:43:01,566

So I just want to say that
fractal phenomenon in nature

784

00:43:01,566 --> 00:43:02,900

is all about us,

785

00:43:02,900 --> 00:43:05,066

including the trees
that surround us

786

00:43:05,066 --> 00:43:06,933

in our beautiful planet,

787

00:43:06,933 --> 00:43:11,400

and would like to acknowledge

788

00:43:11,400 --> 00:43:14,066

the many people
that I've participated with

789

00:43:14,066 --> 00:43:16,700

in this research.

790

00:43:16,700 --> 00:43:21,233

It certainly has been an honor
to work first...

791

00:43:21,233 --> 00:43:22,366

Oop.

792

00:43:26,633 --> 00:43:29,166

This is Patricia Keith
and Mary Vickerman,

793

00:43:29,166 --> 00:43:30,700

the software-development team

794

00:43:30,700 --> 00:43:34,700

with whom I developed
the VESGEN software.

795

00:43:34,700 --> 00:43:37,466

This is our new team
here at Ames,

796

00:43:37,466 --> 00:43:42,200

Ruchi Vyas, Amanda Vu,
and Sneha Rahunandan,

797

00:43:42,200 --> 00:43:44,300

and also,
our long-term collaborator

798

00:43:44,300 --> 00:43:46,900

continues to work with us

on our new studies,

799

00:43:46,900 --> 00:43:50,066

Dr. Krishnan Radhakrishnan.

800

00:43:50,066 --> 00:43:52,933

There have been a number
of biologists, physicians,

801

00:43:52,933 --> 00:43:56,866

and engineers inside NASA
and at these other institutions

802

00:43:56,866 --> 00:43:59,600

who have participated
in these collaborative studies.

803

00:43:59,600 --> 00:44:02,033

So thank you
for your attention.

804

00:44:02,033 --> 00:44:05,233

[applause]

805

00:44:05,233 --> 00:44:07,733

- Thank you very much.
Thank you.

806

00:44:07,733 --> 00:44:09,233

So we have time for questions.

807

00:44:09,233 --> 00:44:11,433

If you have a question,
please raise your hand

808

00:44:11,433 --> 00:44:13,733

and wait for the microphone.

809

00:44:16,900 --> 00:44:18,900

There.

810

00:44:23,000 --> 00:44:26,333

- Hi, Pat. You had mentioned earlier on your presentation

811

00:44:26,333 --> 00:44:29,733

something about increased visual impairment

812

00:44:29,733 --> 00:44:31,833

in tropical zones.

813

00:44:31,833 --> 00:44:35,066

Is that something that you can elaborate on or...?

814

00:44:35,066 --> 00:44:38,033

- Um, well, in the tropics, of course,

815

00:44:38,033 --> 00:44:40,000

light is much more intense.

816

00:44:40,000 --> 00:44:43,066

So I think it's not so much the retinal problems,

817

00:44:43,066 --> 00:44:44,900

but more the opacification

818

00:44:44,900 --> 00:44:47,933

of the anterior portion of the eye,

819

00:44:47,933 --> 00:44:50,033

the cataracts that develop.

820

00:44:50,033 --> 00:44:51,966

But they also
are very interested

821
00:44:51,966 --> 00:44:54,500
in the posterior portion
of the eye, the retina,

822
00:44:54,500 --> 00:44:57,333
because of diabetes,

823
00:44:57,333 --> 00:45:00,800
age-related
macular degeneration,

824
00:45:00,800 --> 00:45:02,766
these other vision diseases

825
00:45:02,766 --> 00:45:04,900
which have
somewhat greater prevalence

826
00:45:04,900 --> 00:45:07,133
in a tropical climate.

827
00:45:13,666 --> 00:45:15,900
- So I have a question.

828
00:45:15,900 --> 00:45:18,166
So, if you look
at the software,

829
00:45:18,166 --> 00:45:20,033
and you sort of
mentioned it before

830
00:45:20,033 --> 00:45:21,966
by starting
and looking at--

831

00:45:21,966 --> 00:45:25,333

basically looking
at the atmosphere,

832

00:45:25,333 --> 00:45:29,200

have you tried applying this
to other types of fields

833

00:45:29,200 --> 00:45:31,000

besides biology,

834

00:45:31,000 --> 00:45:35,566

specifically looking at maybe
earth-science images across--

835

00:45:35,566 --> 00:45:40,233

looking at planets
and other systems like that

836

00:45:40,233 --> 00:45:43,966

to see whether this could be
applied in that source?

837

00:45:43,966 --> 00:45:46,000

- Well, that's
a very interesting question,

838

00:45:46,000 --> 00:45:48,733

and people have suggested
that we look, for example,

839

00:45:48,733 --> 00:45:52,100

at arterial branching systems
in rivers.

840

00:45:52,100 --> 00:45:56,333

When you look at NASA and other
atmospheric photographs

841

00:45:56,333 --> 00:45:59,033

of the branching patterns
of rivers,

842

00:45:59,033 --> 00:46:02,900
or if you're just flying
over the country in a plane,

843

00:46:02,900 --> 00:46:05,133
there's definitely
a similarity, I think,

844

00:46:05,133 --> 00:46:07,266
with vascular branching.

845

00:46:07,266 --> 00:46:11,333
But, of course, it's not being
driven by our pumping hearts.

846

00:46:11,333 --> 00:46:13,066
It is a fluid-based system,
however,

847

00:46:13,066 --> 00:46:16,300
and that's one pattern
that I think has strong analogy.

848

00:46:16,300 --> 00:46:21,000
I have to say that I can't think
of too many others

849

00:46:21,000 --> 00:46:23,900
that have been suggested to us,

850

00:46:23,900 --> 00:46:27,066
but certainly you're very right,
Dr. Cohen,

851

00:46:27,066 --> 00:46:31,333
in the very common presence

852

00:46:31,333 --> 00:46:33,433
of not only branching systems,

853

00:46:33,433 --> 00:46:35,566
but other kinds
of fractal-branching patterns

854

00:46:35,566 --> 00:46:36,866
in nature.

855

00:46:36,866 --> 00:46:40,433
I think they are so common
because they just have--

856

00:46:40,433 --> 00:46:43,400
they have a way of--
space-filling is really

857

00:46:43,400 --> 00:46:46,566
the fundamental concept
of the fractal field.

858

00:46:54,866 --> 00:46:56,266
- Thank you for the talk.

859

00:46:56,266 --> 00:47:01,833
The question I have is for
low gravity and long flight

860

00:47:01,833 --> 00:47:03,333
for the astronaut.

861

00:47:03,333 --> 00:47:06,366
I mean, obviously,
the blood flow--

862

00:47:06,366 --> 00:47:09,300
the branches in your eyes
are most obvious,

863

00:47:09,300 --> 00:47:13,066

but could there also be changes
in other parts of the body

864

00:47:13,066 --> 00:47:15,000

that we don't know yet?

865

00:47:15,000 --> 00:47:17,833

- Yes, that's
a very important question.

866

00:47:17,833 --> 00:47:21,200

People have been researching
the fluid shifts

867

00:47:21,200 --> 00:47:24,000

that are known to occur
in microgravity for some decades

868

00:47:24,000 --> 00:47:28,566

and the impact of that
on the human body.

869

00:47:28,566 --> 00:47:30,800

Of course,
that problem is something

870

00:47:30,800 --> 00:47:32,633

that has been known
for some decades,

871

00:47:32,633 --> 00:47:35,966

because in microgravity,
the fluid shifts in our body

872

00:47:35,966 --> 00:47:39,666

are at the level
of one to two liters

873

00:47:39,666 --> 00:47:42,766

and go to the tops
of our bodies

874

00:47:42,766 --> 00:47:46,566

instead of to the bottoms
of our bodies as on Earth.

875

00:47:48,566 --> 00:47:50,633

I think it's only
with the long-duration flights

876

00:47:50,633 --> 00:47:52,566

that we have begun to initiate

877

00:47:52,566 --> 00:47:55,066

that we're seeing the impact
of these--

878

00:47:55,066 --> 00:47:57,933

adverse impact
of these fluid shifts

879

00:47:57,933 --> 00:48:02,733

on the visual impairments
that appear to be associated

880

00:48:02,733 --> 00:48:05,033

with increased
intracranial pressure.

881

00:48:05,033 --> 00:48:08,900

But again, as we know,
mechanistically, to prove this

882

00:48:08,900 --> 00:48:11,066

and investigate this
is very difficult.

883

00:48:11,066 --> 00:48:12,866
We may have that hypothesis,

884

00:48:12,866 --> 00:48:17,900
but the actual medical studies
are very difficult.

885

00:48:17,900 --> 00:48:20,466
NASA has made it
a high priority.

886

00:48:20,466 --> 00:48:23,366
It's pretty equivalent
to the appreciation

887

00:48:23,366 --> 00:48:26,233
of bone-density losses.

888

00:48:26,233 --> 00:48:28,433
So, therefore,
we are investigating it

889

00:48:28,433 --> 00:48:29,600
with studies such as ours,

890

00:48:29,600 --> 00:48:32,000
but many other studies
by ophthalmologists,

891

00:48:32,000 --> 00:48:34,566
physiologists in the brain,

892

00:48:34,566 --> 00:48:38,766
also the hindlimb unweighted
rodent model is being used

893

00:48:38,766 --> 00:48:41,766
to look at these questions
of the adverse effects

894
00:48:41,766 --> 00:48:43,566
throughout the body

895
00:48:43,566 --> 00:48:44,966
of the fluid shifts

896
00:48:44,966 --> 00:48:48,566
as mediated necessarily
by the small vessels.

897
00:48:53,233 --> 00:48:55,733
- Okay. If there are
no further questions,

898
00:48:55,733 --> 00:48:57,700
please join me
in thanking Dr. Parsons

899
00:48:57,700 --> 00:48:59,100
for an excellent seminar.

900
00:48:59,100 --> 00:49:02,166
[applause]