
AbSciCon
2019

1
00:00:00,790 --> 00:00:07,320
[Music]

2
00:00:11,110 --> 00:00:09,120
[Applause]

3
00:00:12,910 --> 00:00:11,120
alright thanks Jared and thanks for the

4
00:00:16,410 --> 00:00:12,920
organizers for letting me present my

5
00:00:19,840 --> 00:00:16,420
work here so I'm gonna be talking about

6
00:00:21,430 --> 00:00:19,850
the biophysical constraints and modeling

7
00:00:23,830 --> 00:00:21,440
these quantitatively and how we can

8
00:00:25,779 --> 00:00:23,840
actually use this to start to understand

9
00:00:26,439 --> 00:00:25,789
how does it shape the bacterial

10
00:00:29,380 --> 00:00:26,449
metabolomic

11
00:00:31,029 --> 00:00:29,390
so Chris and his talk talked a lot about

12
00:00:32,800 --> 00:00:31,039
these governing constraints where we're

13
00:00:34,570 --> 00:00:32,810

interested in trying to model these

14
00:00:36,160 --> 00:00:34,580
specifically mathematically and see how

15
00:00:39,910 --> 00:00:36,170
some of them work together maybe to

16
00:00:42,700 --> 00:00:39,920
start to constrain the space and like

17
00:00:45,880 --> 00:00:42,710
start off this kind of this talk

18
00:00:47,710 --> 00:00:45,890
thinking about this kind of image by

19
00:00:50,050 --> 00:00:47,720
David Goodsell Scripps Research

20
00:00:51,430 --> 00:00:50,060
Institute where if we look at the cell

21
00:00:53,830 --> 00:00:51,440
it's a crowded place there's a lot of

22
00:00:56,290 --> 00:00:53,840
different things that constrain the

23
00:00:58,030 --> 00:00:56,300
metabolomic cellular function a lot of

24
00:01:00,250 --> 00:00:58,040
them are physical constraints there's a

25
00:01:01,780 --> 00:01:00,260
lot of stuff packed in here all the new

26
00:01:04,450 --> 00:01:01,790
klarik material and proteins and

27
00:01:06,940 --> 00:01:04,460
macromolecules and lipids and what we're

28
00:01:10,420 --> 00:01:06,950
interested in looking at specifically is

29
00:01:11,800 --> 00:01:10,430
the metabolomic eul's involved in energy

30
00:01:14,410 --> 00:01:11,810
metabolism which are too small to even

31
00:01:16,410 --> 00:01:14,420
see on an image like this and so we can

32
00:01:19,390 --> 00:01:16,420
start to think about what sorts of

33
00:01:23,710 --> 00:01:19,400
biophysical laws and principles start to

34
00:01:26,080 --> 00:01:23,720
govern and point to different phenotypic

35
00:01:27,100 --> 00:01:26,090
States now there's a variety of

36
00:01:30,550 --> 00:01:27,110
different constraints that have been

37
00:01:33,580 --> 00:01:30,560
used in the past to model metabolism a

38
00:01:35,320 --> 00:01:33,590

lot of this work is in the field of flux

39
00:01:38,550 --> 00:01:35,330
balance analysis and using constraint

40
00:01:40,480 --> 00:01:38,560
based modeling to model and compute the

41
00:01:41,590 --> 00:01:40,490
genotype-phenotype relationship and when

42
00:01:44,110 --> 00:01:41,600
we talk about that in terms of

43
00:01:47,140 --> 00:01:44,120
metabolism a lot of what these models do

44
00:01:48,670 --> 00:01:47,150
is they compute different feasible flux

45
00:01:52,560 --> 00:01:48,680
states of the network so they compute

46
00:01:54,510 --> 00:01:52,570
pathway usage based on different

47
00:01:57,039 --> 00:01:54,520
different constraints that are

48
00:01:59,680 --> 00:01:57,049
mathematically expressed based on

49
00:02:02,770 --> 00:01:59,690
measured omics data and so some of these

50
00:02:04,350 --> 00:02:02,780
types of constraints come from gene

51
00:02:07,180 --> 00:02:04,360
expression and protein expression

52
00:02:08,380 --> 00:02:07,190
metabolomics data and if we have

53
00:02:10,539 --> 00:02:08,390
information available on different

54
00:02:12,070 --> 00:02:10,549
kinetic parameters we can model these

55
00:02:13,539 --> 00:02:12,080
mathematically and we can integrate this

56
00:02:17,619 --> 00:02:13,549
in with the structure of the metabolic

57
00:02:20,500 --> 00:02:17,629
Network and then we can compute a

58
00:02:22,300 --> 00:02:20,510
solution space where each point in this

59
00:02:24,280 --> 00:02:22,310
space would represent a

60
00:02:26,290 --> 00:02:24,290
double flux state of the network so each

61
00:02:29,589 --> 00:02:26,300
point represents different pathway usage

62
00:02:32,199 --> 00:02:29,599
and as we add these constraints we start

63
00:02:35,080 --> 00:02:32,209

to zero in on a by physically and

64
00:02:38,050 --> 00:02:35,090
physiologically relevant set of fluxes

65
00:02:40,180 --> 00:02:38,060
and eventually we can optimize and

66
00:02:41,800 --> 00:02:40,190
compute maybe a maximal growth rate and

67
00:02:43,120 --> 00:02:41,810
then look and see well for this given

68
00:02:45,610 --> 00:02:43,130
growth rate and the data that we have

69
00:02:49,930 --> 00:02:45,620
this is what we would predict the flux

70
00:02:51,490 --> 00:02:49,940
State to be but in these models most of

71
00:02:53,589 --> 00:02:51,500
what is missing are a lot of these

72
00:02:55,600 --> 00:02:53,599
biophysical constraints so when we model

73
00:02:58,030 --> 00:02:55,610
in this kind of framework we're really

74
00:02:59,590 --> 00:02:58,040
assuming away things like pH and maybe

75
00:03:01,740 --> 00:02:59,600
some kind of spatial constraints and all

76
00:03:03,640 --> 00:03:01,750
of these sorts of energetics and

77
00:03:06,880 --> 00:03:03,650
electroneutrality and all these sorts of

78
00:03:09,729 --> 00:03:06,890
things that do obviously play a role and

79
00:03:11,860 --> 00:03:09,739
so the goal here is to translate some of

80
00:03:14,860 --> 00:03:11,870
these governing biophysical constraints

81
00:03:16,240 --> 00:03:14,870
into quantitative values so some kind of

82
00:03:18,280 --> 00:03:16,250
mathematical form that can help us

83
00:03:20,320 --> 00:03:18,290
integrate in with the network structure

84
00:03:22,539 --> 00:03:20,330
and actually compute functional states

85
00:03:24,370 --> 00:03:22,549
and ideally we're able to do this and

86
00:03:26,440 --> 00:03:24,380
then look at different environments

87
00:03:28,270 --> 00:03:26,450
either existing ones that we can model

88
00:03:32,440 --> 00:03:28,280

and measure or maybe theoretical

89
00:03:33,490 --> 00:03:32,450
environments and so most of what I'm

90
00:03:35,380 --> 00:03:33,500
going to talk about today is a

91
00:03:37,809 --> 00:03:35,390
theoretical framework that we've put

92
00:03:39,520 --> 00:03:37,819
together that allows us to model we've

93
00:03:40,870 --> 00:03:39,530
put together ten different classes of

94
00:03:42,640 --> 00:03:40,880
constraints eight of these are really

95
00:03:44,880 --> 00:03:42,650
biophysical constraints then we have a

96
00:03:47,830 --> 00:03:44,890
couple constraints that we use to

97
00:03:49,840 --> 00:03:47,840
address technological issues with

98
00:03:51,640 --> 00:03:49,850
integrating data like this into a

99
00:03:52,930 --> 00:03:51,650
framework like this so I'm not going to

100
00:03:54,699 --> 00:03:52,940
spend a ton of time this is very dense

101
00:03:57,009 --> 00:03:54,709
image but a couple things that I want to

102
00:03:59,259 --> 00:03:57,019
point out is we've formulated all of

103
00:04:01,090 --> 00:03:59,269
these constrains with only a single free

104
00:04:02,920 --> 00:04:01,100
variable and that's X the metabolite

105
00:04:05,770 --> 00:04:02,930
concentration all of the other

106
00:04:07,660 --> 00:04:05,780
parameters are either measured values

107
00:04:10,180 --> 00:04:07,670
things like the turgor pressure for a

108
00:04:13,210 --> 00:04:10,190
given system membrane potential ionic

109
00:04:14,590 --> 00:04:13,220
strength of the solution or they are in

110
00:04:17,050 --> 00:04:14,600
the case of like thermodynamics for

111
00:04:18,969 --> 00:04:17,060
example these are Gibbs free energies of

112
00:04:20,770 --> 00:04:18,979
formation for individual compounds and

113
00:04:25,659 --> 00:04:20,780

these are quantities that can be

114
00:04:26,890 --> 00:04:25,669
computed or some measured and so when we

115
00:04:29,440 --> 00:04:26,900
started to try to put together this

116
00:04:31,120 --> 00:04:29,450
framework that was one of the the first

117
00:04:34,089 --> 00:04:31,130
issues is where do we get that kind of

118
00:04:35,950 --> 00:04:34,099
data and so some some work by some of my

119
00:04:38,680 --> 00:04:35,960
colleagues in my dissertation lab

120
00:04:40,210 --> 00:04:38,690
spent some time and we used an updated

121
00:04:42,580 --> 00:04:40,220
group contribution method to estimate

122
00:04:44,080 --> 00:04:42,590
some of these necessary parameters some

123
00:04:46,900 --> 00:04:44,090
of these thermodynamic quantities that

124
00:04:49,450 --> 00:04:46,910
allow us to parameterize everything I

125
00:04:52,810 --> 00:04:49,460
just showed you on the last slide and of

126
00:04:54,520 --> 00:04:52,820
course using constraints to look at

127
00:04:57,100 --> 00:04:54,530
these sorts of things is not novel

128
00:04:58,629 --> 00:04:57,110
really the novelty here we hope is to

129
00:05:00,040 --> 00:04:58,639
try to integrate all of these

130
00:05:01,659 --> 00:05:00,050
constraints together into a single

131
00:05:03,730 --> 00:05:01,669
unified framework to start to look at

132
00:05:05,860 --> 00:05:03,740
some of these things but certainly just

133
00:05:08,230 --> 00:05:05,870
looking at thermodynamics and some of

134
00:05:11,020 --> 00:05:08,240
these thermal properties has been done

135
00:05:13,689 --> 00:05:11,030
previously and extensively and some

136
00:05:16,270 --> 00:05:13,699
recent work from our lab used these

137
00:05:18,820 --> 00:05:16,280
computed parameters to look at the

138
00:05:20,409 --> 00:05:18,830

evolution the evolutionary trajectory of

139
00:05:21,879 --> 00:05:20,419
different pathways based on

140
00:05:24,700 --> 00:05:21,889
thermodynamic feasibility and some of

141
00:05:27,969 --> 00:05:24,710
the more interesting outcomes from that

142
00:05:30,219 --> 00:05:27,979
study was that for two different

143
00:05:32,290 --> 00:05:30,229
organisms living in different niches for

144
00:05:34,210 --> 00:05:32,300
them to produce the same biomass

145
00:05:36,040 --> 00:05:34,220
precursor they might have substantially

146
00:05:37,990 --> 00:05:36,050
different pathway usage and it's based

147
00:05:39,310 --> 00:05:38,000
on environmental conditions and if we

148
00:05:42,279 --> 00:05:39,320
can start to model that we can start to

149
00:05:43,750 --> 00:05:42,289
understand maybe why one organism might

150
00:05:47,020 --> 00:05:43,760
use one route and one might use another

151
00:05:49,659 --> 00:05:47,030
and ultimately it came down one of the

152
00:05:50,860 --> 00:05:49,669
observations is that these different

153
00:05:54,000 --> 00:05:50,870
pathways might depend on different

154
00:05:57,279 --> 00:05:54,010
cofactors and those are different

155
00:05:59,500 --> 00:05:57,289
important parameters that can affect

156
00:06:03,279 --> 00:05:59,510
based on the environmental conditions

157
00:06:05,290 --> 00:06:03,289
what sort of pathways the other thing i

158
00:06:07,149 --> 00:06:05,300
want to comment about this framework

159
00:06:08,890 --> 00:06:07,159
we've put together is that some of the

160
00:06:11,230 --> 00:06:08,900
models we were using to look at

161
00:06:12,370 --> 00:06:11,240
individual constraints are fairly high

162
00:06:14,649 --> 00:06:12,380
level and if you do have a more

163
00:06:16,750 --> 00:06:14,659

sophisticated model this framework is

164
00:06:18,040 --> 00:06:16,760
modular so for example some separate

165
00:06:19,270 --> 00:06:18,050
work we're doing is to look at the

166
00:06:21,430 --> 00:06:19,280
membrane potential and we want to

167
00:06:23,560 --> 00:06:21,440
integrate membrane potential as a

168
00:06:25,480 --> 00:06:23,570
constraint when we're interested in

169
00:06:29,320 --> 00:06:25,490
computing these phenotypic States for

170
00:06:33,899 --> 00:06:29,330
these cells and so we've built a model

171
00:06:36,279 --> 00:06:33,909
of the spatial model of the membrane and

172
00:06:40,260 --> 00:06:36,289
for the human red blood cell there's a

173
00:06:42,879 --> 00:06:40,270
lot of data available for the

174
00:06:45,459 --> 00:06:42,889
phospholipid composition of the lipid

175
00:06:47,050 --> 00:06:45,469
bilayer and so for this for this

176
00:06:48,610 --> 00:06:47,060
framework the free variable here that

177
00:06:49,839 --> 00:06:48,620
we're looking at is the individual

178
00:06:51,579 --> 00:06:49,849
concentrations of all of the

179
00:06:54,760 --> 00:06:51,589
lipids in the network and so you can

180
00:06:56,469 --> 00:06:54,770
actually determine from available

181
00:06:58,809 --> 00:06:56,479
measured data we were able to compute

182
00:07:01,029 --> 00:06:58,819
how much sphingomyelin or

183
00:07:03,309 --> 00:07:01,039
phosphatidylserine is on one side of the

184
00:07:04,570 --> 00:07:03,319
lipid or the other of the bilayer or the

185
00:07:05,889 --> 00:07:04,580
other and then we can compute the

186
00:07:07,959 --> 00:07:05,899
potential and then we can integrate this

187
00:07:11,379 --> 00:07:07,969
in with this larger genome scale

188
00:07:13,480 --> 00:07:11,389

framework and see well given a specific

189
00:07:15,699 --> 00:07:13,490
set of phospholipids given this membrane

190
00:07:17,379 --> 00:07:15,709
composition how does that constrain

191
00:07:19,299 --> 00:07:17,389
metabolism or we could ask the other

192
00:07:21,100 --> 00:07:19,309
question which is what would we want

193
00:07:24,579 --> 00:07:21,110
metabolism to look like in order to

194
00:07:26,949 --> 00:07:24,589
generate a specific phospholipid

195
00:07:29,199 --> 00:07:26,959
composition for example and so again

196
00:07:30,579 --> 00:07:29,209
this is also a work in progress but just

197
00:07:32,169 --> 00:07:30,589
to say that if you have a more

198
00:07:33,699 --> 00:07:32,179
sophisticated model and better

199
00:07:34,959 --> 00:07:33,709
measurements for some of these different

200
00:07:36,429 --> 00:07:34,969
constraints and you think about them in

201
00:07:39,699 --> 00:07:36,439
different ways this sort of framework

202
00:07:40,659 --> 00:07:39,709
could encapsulate that sort of thing one

203
00:07:42,070 --> 00:07:40,669
of the other constraints that I

204
00:07:44,379 --> 00:07:42,080
mentioned that is a very important one

205
00:07:46,029 --> 00:07:44,389
when we're talking about modeling and

206
00:07:47,949 --> 00:07:46,039
computing these phenotypic States is

207
00:07:51,429 --> 00:07:47,959
accounting for the effect of pH on small

208
00:07:53,169 --> 00:07:51,439
molecules and so when we talk about in

209
00:07:55,659 --> 00:07:53,179
kind of broad terms these metabolic

210
00:08:00,670 --> 00:07:55,669
networks we really just think of

211
00:08:02,259 --> 00:08:00,680
metabolites as ATP but in reality ATP

212
00:08:03,969 --> 00:08:02,269
exists as one of many different

213
00:08:05,439 --> 00:08:03,979

protonation states that is possible

214
00:08:08,439 --> 00:08:05,449
based on a lot of different things in

215
00:08:10,719 --> 00:08:08,449
the network and as the pH of the system

216
00:08:13,029 --> 00:08:10,729
changes there's a different dominant

217
00:08:14,829 --> 00:08:13,039
species of ATP might be bound to

218
00:08:18,969 --> 00:08:14,839
magnesium or a different charged state

219
00:08:21,489 --> 00:08:18,979
and so this is again one of the

220
00:08:23,230 --> 00:08:21,499
constraints that we're using - based on

221
00:08:25,839 --> 00:08:23,240
the pH of the system we can modulate

222
00:08:30,790 --> 00:08:25,849
which of the metabolite species are most

223
00:08:32,769 --> 00:08:30,800
dominant so we're currently in the

224
00:08:34,089 --> 00:08:32,779
process of applying this framework to

225
00:08:35,649 --> 00:08:34,099
look at different case studies one of

226
00:08:37,029 --> 00:08:35,659
the first case studies that I'm going to

227
00:08:41,319 --> 00:08:37,039
talk about here in my limited time today

228
00:08:45,249 --> 00:08:41,329
is modeling ecoli an exponential growth

229
00:08:46,660 --> 00:08:45,259
at pH of 7.5 and so we're currently in

230
00:08:48,249 --> 00:08:46,670
the process of scaling up to genome

231
00:08:49,360 --> 00:08:48,259
scale and right now we've been tuning

232
00:08:51,610 --> 00:08:49,370
these parameters and looking at these

233
00:08:53,470 --> 00:08:51,620
constraints on a smaller version of the

234
00:08:56,259 --> 00:08:53,480
network that contains glycolysis and the

235
00:08:59,650 --> 00:08:56,269
TCA cycle so total about 45 metabolites

236
00:09:01,780 --> 00:08:59,660
and what I'm showing here this is the

237
00:09:02,980 --> 00:09:01,790
same data on the top it's an absolute

238
00:09:04,040 --> 00:09:02,990

scale and on the bottom it's on the log

239
00:09:05,720 --> 00:09:04,050
scale

240
00:09:08,660 --> 00:09:05,730
so what I'm showing here is we've

241
00:09:11,420 --> 00:09:08,670
computed the these bars represents the

242
00:09:12,860 --> 00:09:11,430
minimum and the maximum feasible

243
00:09:16,610 --> 00:09:12,870
concentration according to these

244
00:09:19,790 --> 00:09:16,620
constraints that we've laid out and then

245
00:09:21,740 --> 00:09:19,800
the yellow points here are data that has

246
00:09:25,579 --> 00:09:21,750
been measured in the literature from

247
00:09:28,009 --> 00:09:25,589
Joshua Bennett Rabinowitz his lab and we

248
00:09:30,139 --> 00:09:28,019
can map that on and start to see how

249
00:09:31,519 --> 00:09:30,149
well does this do these mathematical

250
00:09:33,430 --> 00:09:31,529
constraints work out how well do they

251
00:09:35,660 --> 00:09:33,440
play together

252
00:09:37,819 --> 00:09:35,670
we're still fine-tuning some things but

253
00:09:39,379 --> 00:09:37,829
certainly one thing that we've been able

254
00:09:40,430 --> 00:09:39,389
to notice so far is that the upper

255
00:09:43,400 --> 00:09:40,440
bounds on a lot of these different

256
00:09:44,960 --> 00:09:43,410
metabolite concentrations has been

257
00:09:46,970 --> 00:09:44,970
modulated by the different constraints

258
00:09:48,829 --> 00:09:46,980
and we've performed some sensitivity

259
00:09:52,160 --> 00:09:48,839
analysis to start to see how did those

260
00:09:53,269 --> 00:09:52,170
start to to change and certainly one of

261
00:09:55,400 --> 00:09:53,279
the the next things that we're going to

262
00:09:56,840 --> 00:09:55,410
try to figure out is why in this current

263
00:09:58,970 --> 00:09:56,850

framework do some of these lower bounds

264
00:10:01,069 --> 00:09:58,980
all just kind of map all the way to zero

265
00:10:02,600 --> 00:10:01,079
there's got to be some lower bound on

266
00:10:04,970 --> 00:10:02,610
those so that's that's part of where the

267
00:10:08,090 --> 00:10:04,980
the current status of this work is and

268
00:10:09,829 --> 00:10:08,100
once we've defined this very complex

269
00:10:11,389 --> 00:10:09,839
optimization problem that we use to

270
00:10:12,769 --> 00:10:11,399
compute this space really we're

271
00:10:15,410 --> 00:10:12,779
interested in characterizing in this

272
00:10:16,610 --> 00:10:15,420
space is the first step and so there's

273
00:10:18,379 --> 00:10:16,620
some interesting questions that we can

274
00:10:20,900 --> 00:10:18,389
start to look at once we've built these

275
00:10:22,790 --> 00:10:20,910
constraints and really the goal here is

276
00:10:25,100 --> 00:10:22,800
to try to identify how do these

277
00:10:26,480 --> 00:10:25,110
different constraints interact with each

278
00:10:28,040 --> 00:10:26,490
other are there some constraints that

279
00:10:29,900 --> 00:10:28,050
are more dominant than others and under

280
00:10:32,540 --> 00:10:29,910
certain conditions and so for example we

281
00:10:34,370 --> 00:10:32,550
can look at things like the buffer

282
00:10:36,710 --> 00:10:34,380
capacity as a function of total

283
00:10:39,920 --> 00:10:36,720
metabolite concentration and see so if

284
00:10:42,079 --> 00:10:39,930
this if the color bar here represents

285
00:10:43,879 --> 00:10:42,089
the specific concentration of that

286
00:10:46,220 --> 00:10:43,889
individual metabolite we can see how its

287
00:10:48,500 --> 00:10:46,230
buffer capacity might change in the

288
00:10:51,980 --> 00:10:48,510

context of all of the constraints for

289
00:10:53,569 --> 00:10:51,990
the whole network and see how the but

290
00:10:56,929 --> 00:10:53,579
that might affect a property like the

291
00:10:59,120 --> 00:10:56,939
buffer capacity and like I mentioned the

292
00:11:00,650 --> 00:10:59,130
more interesting part of once we're able

293
00:11:02,030 --> 00:11:00,660
to characterize this network is to see

294
00:11:04,040 --> 00:11:02,040
how did these different

295
00:11:06,620 --> 00:11:04,050
bounds once we've computed them how do

296
00:11:08,689 --> 00:11:06,630
they change as we modulate some maybe of

297
00:11:10,819 --> 00:11:08,699
the global measured parameters like the

298
00:11:12,980 --> 00:11:10,829
turgor pressure if we were to change the

299
00:11:15,230 --> 00:11:12,990
turgor pressure does that maybe modulate

300
00:11:17,240 --> 00:11:15,240
one of the upper bounds if we change the

301
00:11:19,369 --> 00:11:17,250
pH certainly the ratios

302
00:11:22,280 --> 00:11:19,379
different protonation states of the same

303
00:11:24,439 --> 00:11:22,290
metabolite would change and ultimately

304
00:11:25,879 --> 00:11:24,449
then we can begin to answer the question

305
00:11:28,490 --> 00:11:25,889
how to constraints work together to

306
00:11:31,280 --> 00:11:28,500
constrain them at a below so looking

307
00:11:33,410 --> 00:11:31,290
ahead a lot of our interest in this kind

308
00:11:35,090 --> 00:11:33,420
of framework as engineers is what can we

309
00:11:37,220 --> 00:11:35,100
engineer them at abalone so if we can

310
00:11:39,710 --> 00:11:37,230
characterize this space can we start to

311
00:11:41,179 --> 00:11:39,720
maybe predict how do maybe gene

312
00:11:44,210 --> 00:11:41,189
knockouts or a change in media

313
00:11:47,360 --> 00:11:44,220

composition begin to alter this this

314
00:11:50,119 --> 00:11:47,370
feasible state and and perhaps for an

315
00:11:52,730 --> 00:11:50,129
audience here what can these by physical

316
00:11:54,769 --> 00:11:52,740
constraints teach us about different

317
00:11:57,590 --> 00:11:54,779
states of metabolism and why do certain

318
00:11:59,360 --> 00:11:57,600
metabolites like tree hollows for

319
00:12:01,340 --> 00:11:59,370
example act as awesome regulators in

320
00:12:02,720 --> 00:12:01,350
different systems is this framework

321
00:12:06,139 --> 00:12:02,730
something that we can begin to start to

322
00:12:07,639 --> 00:12:06,149
ask and answer questions like these so

323
00:12:09,829 --> 00:12:07,649
just to summarize we've described a

324
00:12:11,960 --> 00:12:09,839
framework that allows for the

325
00:12:13,670 --> 00:12:11,970
translation of governing biophysical

326
00:12:15,949 --> 00:12:13,680
constrains into a mathematical framework

327
00:12:18,530 --> 00:12:15,959
that we're then going to use to compute

328
00:12:20,210 --> 00:12:18,540
functional metabolic states and what

329
00:12:22,850 --> 00:12:20,220
we're attempting to do next is to

330
00:12:24,740 --> 00:12:22,860
compute this to characterize this space

331
00:12:26,179 --> 00:12:24,750
through computation through computation

332
00:12:28,369 --> 00:12:26,189
and look at the feasibility of different

333
00:12:30,710 --> 00:12:28,379
metabolic configurations and theoretical

334
00:12:32,179 --> 00:12:30,720
or hypothesized environments and even

335
00:12:32,960 --> 00:12:32,189
have the capacity once we characterize

336
00:12:34,910 --> 00:12:32,970
this space

337
00:12:37,549 --> 00:12:34,920
- perhaps generate in silico

338
00:12:39,290 --> 00:12:37,559

metabolomics datasets that would at

339
00:12:42,379 --> 00:12:39,300
least obey all of the biophysical laws

340
00:12:44,689 --> 00:12:42,389
that we've laid out here so I'd like to

341
00:12:45,920 --> 00:12:44,699
finish by thanking my colleagues in this

342
00:12:49,400 --> 00:12:45,930
endeavor so this is work that I had

343
00:12:52,309 --> 00:12:49,410
started in my PhD and since I've left

344
00:12:54,079 --> 00:12:52,319
has been taken over by a mirror and

345
00:12:56,389 --> 00:12:54,089
obviously we'd also like to thank my

346
00:12:56,990 --> 00:12:56,399
doctoral adviser professor Paulson at UC

347
00:12:58,759 --> 00:12:57,000
San Diego

348
00:13:01,009 --> 00:12:58,769
and Dan's elinsky has also been

349
00:13:02,269 --> 00:13:01,019
instrumental in guiding this work of

350
00:13:04,939 --> 00:13:02,279
course like would would like to thank

351
00:13:06,530 --> 00:13:04,949
the Novo Nordisk Foundation Center for

352
00:13:08,809 --> 00:13:06,540
by sustainability and my fellowship here

353
00:13:10,970 --> 00:13:08,819
at the Institute for systems biology in

354
00:13:16,639 --> 00:13:10,980
Seattle for funding and with that I will

355
00:13:23,340 --> 00:13:19,500
it one quick question while we get set

356
00:13:28,380 --> 00:13:23,350
up for the next speaker there's a mic up

357
00:13:31,850 --> 00:13:28,390
at the front or so I I kind of wonder if

358
00:13:33,060 --> 00:13:31,860
you're generating hypotheses predictions

359
00:13:36,360 --> 00:13:33,070
explanations

360
00:13:38,460 --> 00:13:36,370
I mean you I mean you you sort of it's

361
00:13:40,980 --> 00:13:38,470
really cool and amazing I just wonder if

362
00:13:42,449 --> 00:13:40,990
if you believe the answers or you

363
00:13:45,090 --> 00:13:42,459

convince the answers I don't need to

364
00:13:47,400 --> 00:13:45,100
take any more measurements or do work or

365
00:13:49,050 --> 00:13:47,410
you know or or maybe we should take new

366
00:13:50,759 --> 00:13:49,060
measurements to validate the model you

367
00:13:52,079 --> 00:13:50,769
have so I think that last point is

368
00:13:53,579 --> 00:13:52,089
actually really what we're trying to get

369
00:13:55,440 --> 00:13:53,589
at is so certainly measuring

370
00:13:58,019 --> 00:13:55,450
metabolomics data and mapping onto this

371
00:13:59,759 --> 00:13:58,029
space can tell us something so many of

372
00:14:01,620 --> 00:13:59,769
those points about 80% were within the

373
00:14:03,660 --> 00:14:01,630
ranges we computed some of them were

374
00:14:05,759 --> 00:14:03,670
outside those ranges and so obviously we

375
00:14:07,829 --> 00:14:05,769
need to tune the network but likely we

376
00:14:09,600 --> 00:14:07,839
will potentially need more data in order

377
00:14:11,130 --> 00:14:09,610
to better fine-tune these constraints

378
00:14:12,840 --> 00:14:11,140
another interesting thing to think about

379
00:14:15,449 --> 00:14:12,850
is are there other constraints that

380
00:14:17,490 --> 00:14:15,459
we're not considering that cause our

381
00:14:20,550 --> 00:14:17,500
predictions to be off and so ultimately

382
00:14:21,990 --> 00:14:20,560
we would like to use this for hypothesis

383
00:14:23,340 --> 00:14:22,000
generation but that's I think a little

384
00:14:25,259 --> 00:14:23,350
ways down the road first we really need

385
00:14:25,710 --> 00:14:25,269
to validate this and exactly to your

386
00:14:26,939 --> 00:14:25,720
point

387
00:14:30,960 --> 00:14:26,949
can we trust what we're actually

388
00:14:33,550 --> 00:14:30,970

computing here all right thank you thank