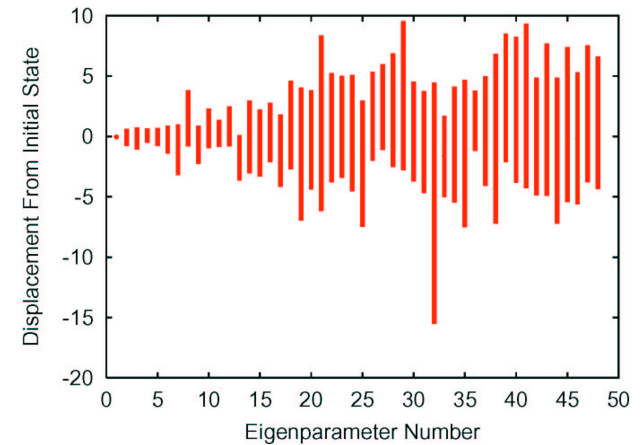
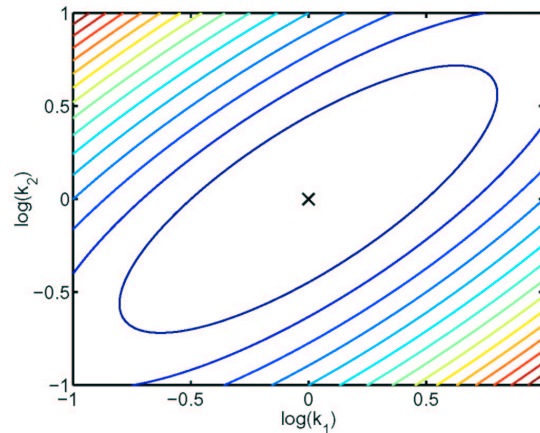
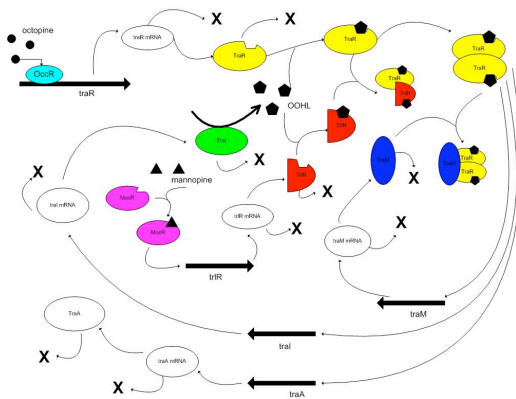


Statistical Mechanics of Sloppy Models



Bacterial Cell-Cell Communication and More

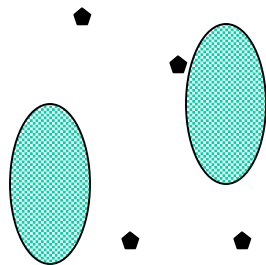
Josh Waterfall, Jim Sethna, Steve Winans



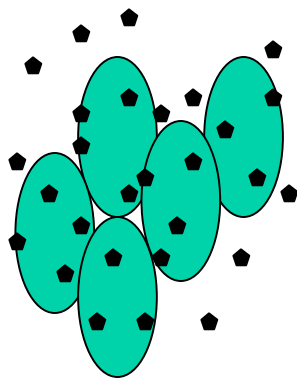
Quorum Sensing

- Cell-cell signaling network for monitoring population density

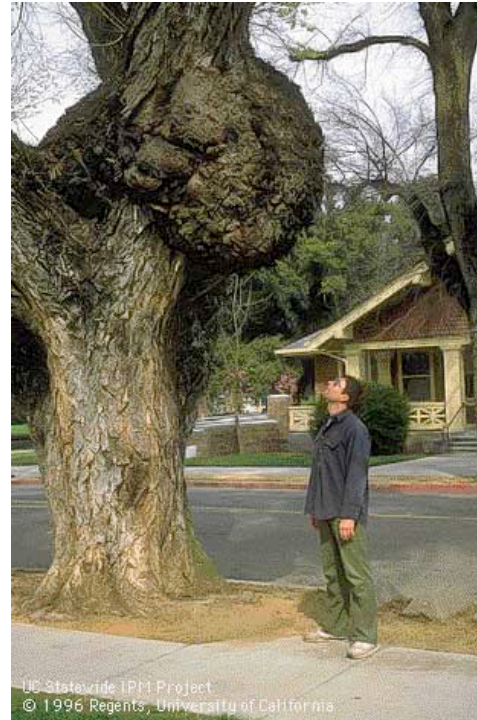
Low population density:
pheromone molecule lost to environment.



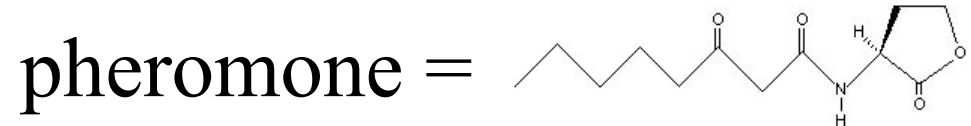
High density:
pheromone is picked up from neighbors and signaling pathway is activated.



Agrobacterium tumefaciens

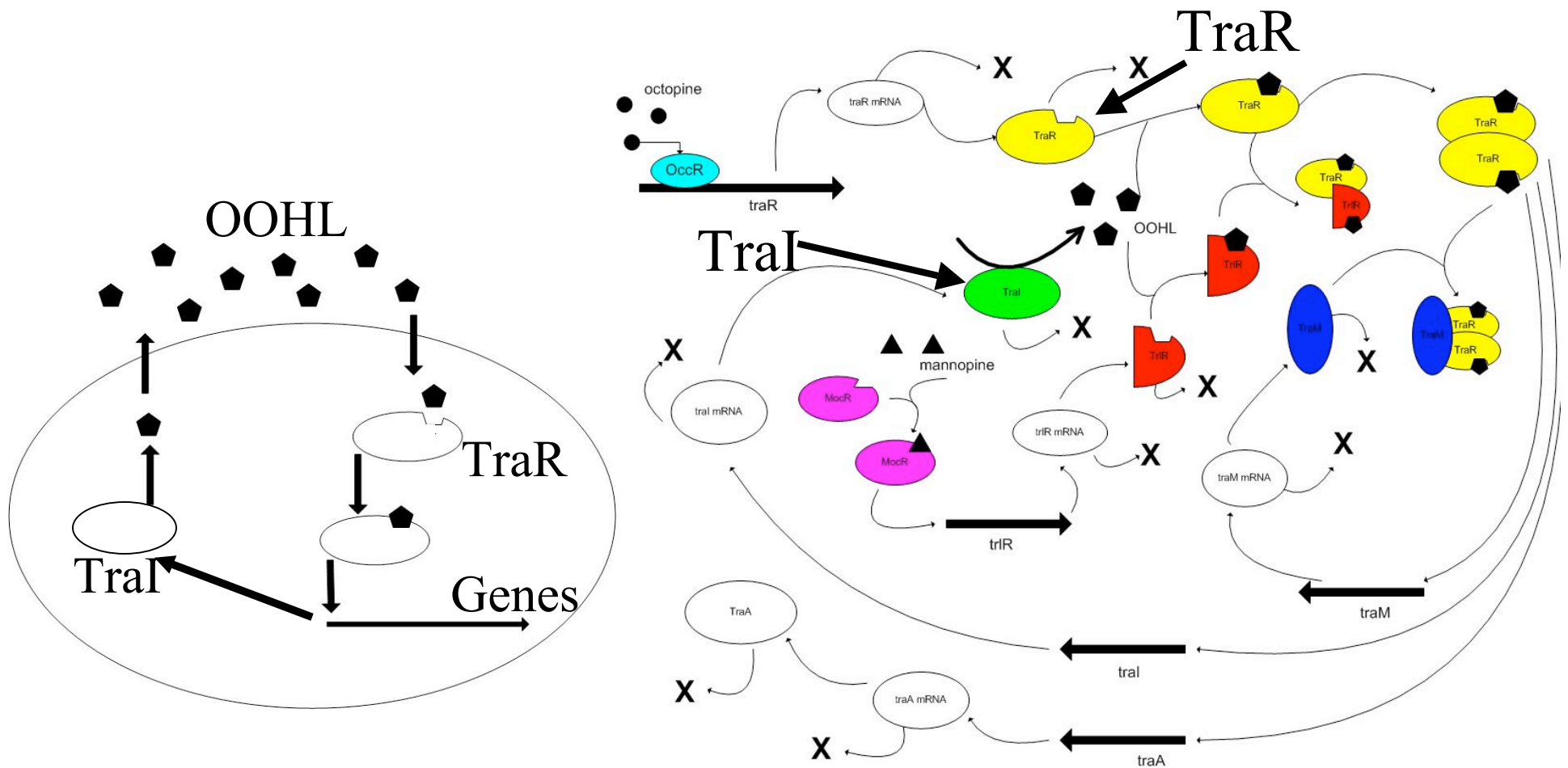


plant pathogen -
transfers
oncogenic DNA
to plant, co-
opting plant
machinery to
make nutrients.



Quorum triggers sharing
of tumor inducing
plasmid

- TraI synthesizes small molecule (OOHL) at low, basal rate
- TraR needs OOHL to fold properly
- Active TraR turns on transcription of other genes, including *traI*
- Hierarchically regulated by separate systems (opine and phenolic compound metabolism)

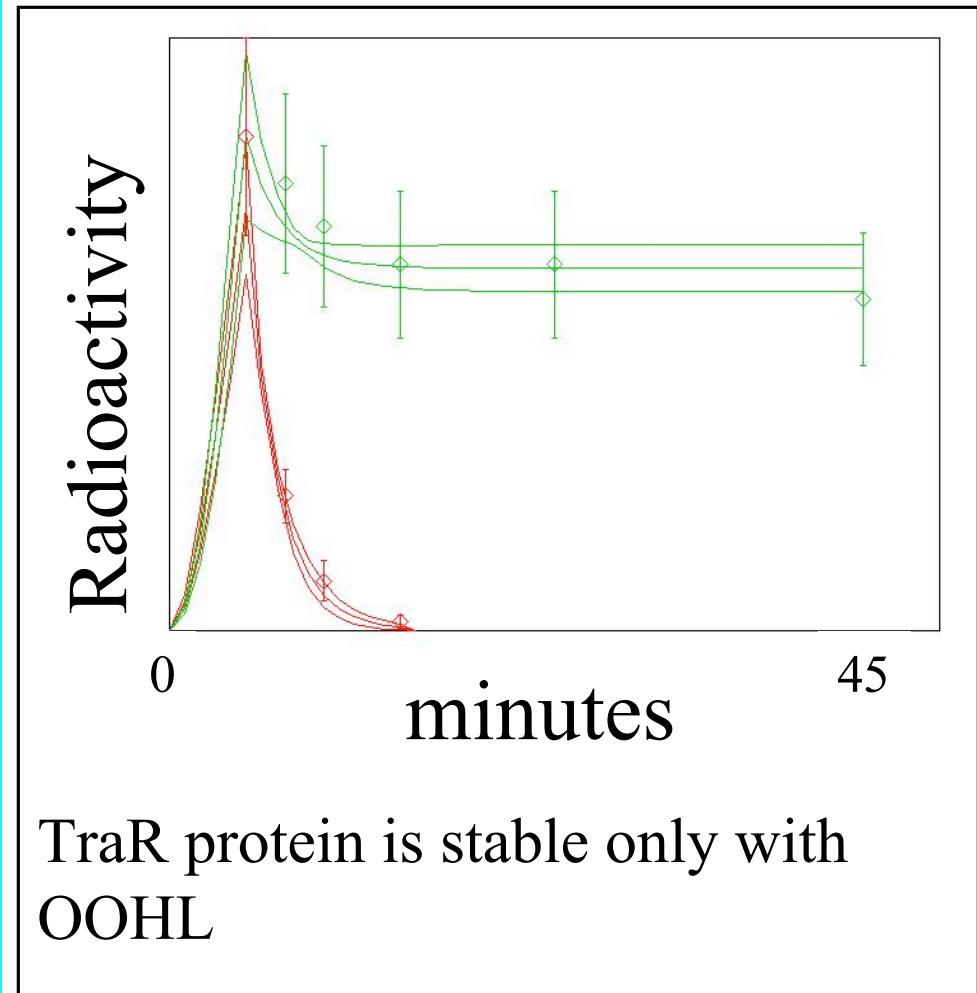


24 Parameter “Fit” to Data

- Cost _ Energy

$$C(\theta) = \frac{1}{2} \sum_{i=1}^{N_R} \frac{(y(\theta) - y_i)^2}{\sigma_i^2}$$

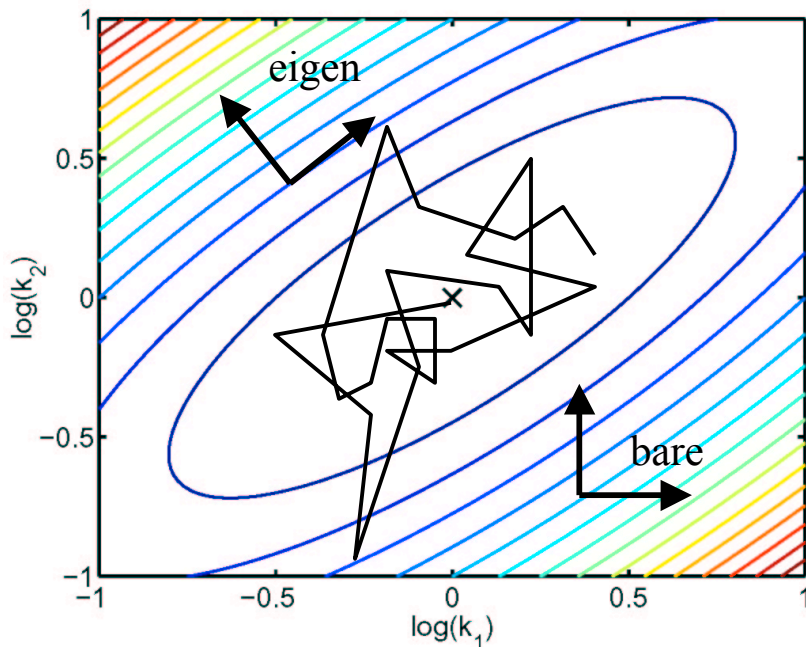
- Also fit to six other sets of genetic and biochemical experiments (38 data points)
- Still misses data
- Hand-tuning, then fancy optimizations
- How much can the fit parameters vary, and still fit the data? (Will give error bars)



Ensemble of Models

We want to consider not just minimum cost solutions, but all solutions consistent with the available data. New level of abstraction: *statistical mechanics in model space*.

- Huge range of scales from stiff to sloppy : 1 inch = 10^3 miles
- Eigendirections not aligned with bare parameters



Generate an ensemble of states with Boltzmann weights $\exp(-C/T)$ and compute for an observable:

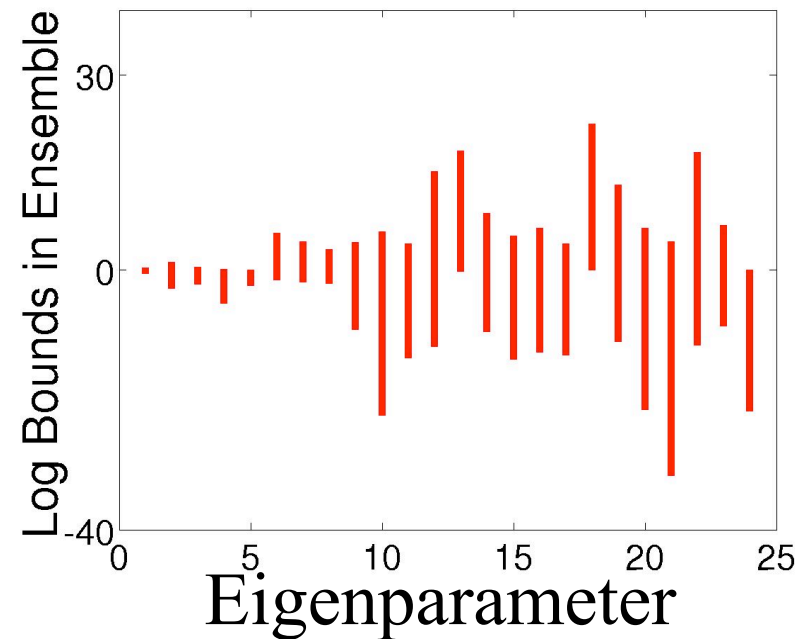
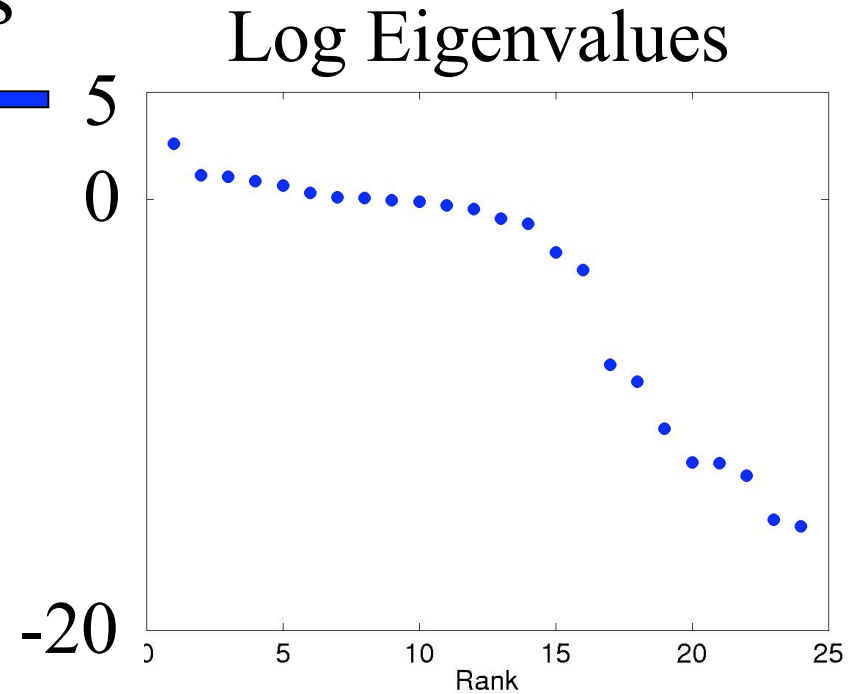
$$\langle O \rangle = \frac{1}{N_E} \sum_{i=1}^{N_E} O(\theta_i^{\mathbf{r}})$$
$$\sigma_O^2 = \langle O^2(\theta^{\mathbf{r}}) \rangle - \langle O(\theta^{\mathbf{r}}) \rangle^2$$

O is chemical concentration, or rate constant ...

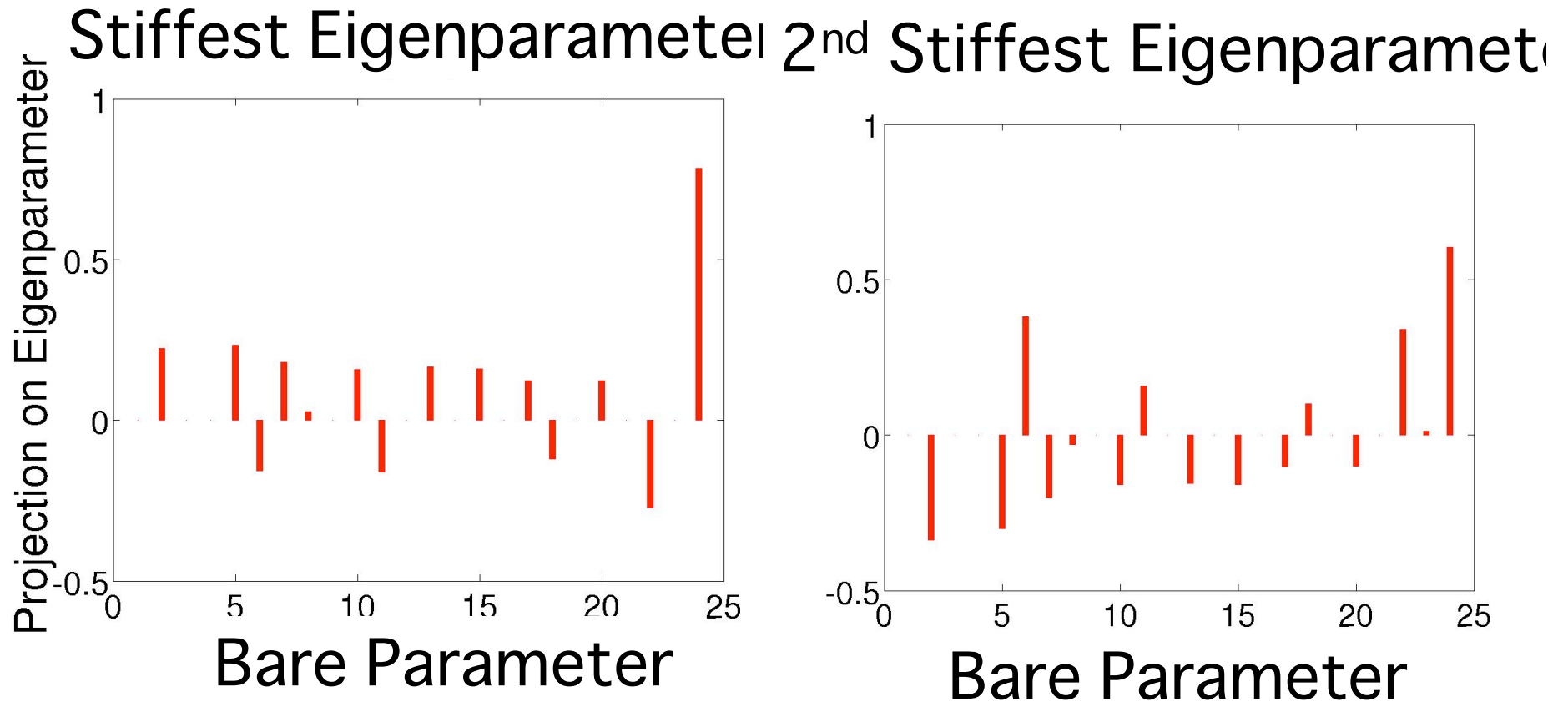
Wide range of natural scales

Eigenvalues – not all parameters are created equal. Range of e^{20} !

Sloppiness – fluctuations in eigenparameters in ensemble up to tens of orders of magnitude!



Biological insight from eigenparameters



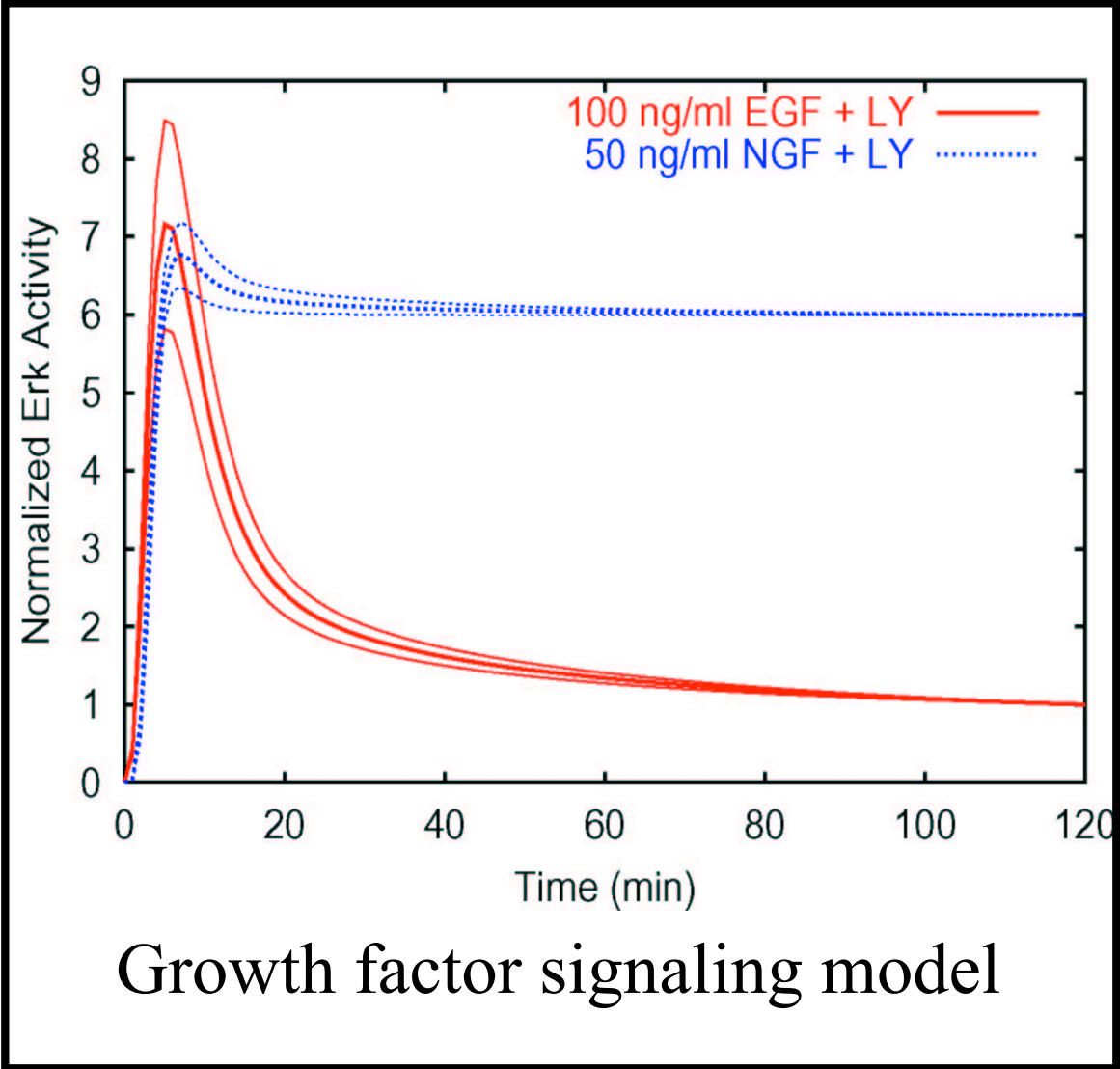
Stiffest eigenparameter
predominantly bacterial
doubling time

Second stiffest adds ratio
between production of TraR
and degradation of TraR and
OOHL

Predictions for experiments are constrained



Although rate constant values are wildly undetermined, predictions for new experiments are not (always).



Other Sloppy systems past, present, future

- Growth Factor Signaling
- Receptor Trafficking
- Translation Dynamics
- Transcription Dynamics
- E-Coli Whole Cell Model
- Nitrogen Cycle in Forests
- Radioactive decay
- Classical Potentials: Molybdenum



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