GSTDMB 2012: DYNAMICAL MODELLING FOR BIOLOGY AND MEDICINE

Lecture 4
Parameter estimation and sensitivity analysis

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Systems approach: basic questions

- Given experimental data, and a mathematical model, what can we infer about the nature of the underlying mechanisms?
- More specifically: can we use the data to determine plausible values for the model parameters? ***Inference***.
- If we can infer a 'reasonable' set of parameters, how do we know whether or not we can trust them? How sensitive is the behaviour of the model to changes in the parameter values? ***Parameter sensitivity***.

Parameter estimation

If we have an ODE model

$$\frac{dx_i}{dt}(t) = f_i\left(\left\{x_{\langle i\rangle}(t)\right\}, \mathbf{p}_i\right); \quad x_i(0) = x_{i0}, i = 1,2,...,n$$

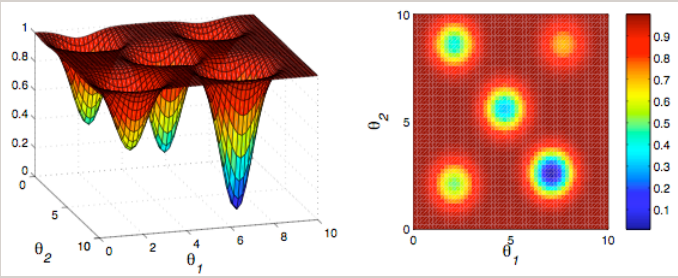
how do we estimate parameters given some experimental data (values of some of the variables x_i at times t_j)?

Seek parameters that minimise the sum of the squared difference between available data and corresponding model variables (the **cost function**):

$$E = \sum_i \sum_j \left(x_i(t_j) - x_i^{data}(t_j)\right)^2$$

For models with a small number of parameters, manual tuning can work well. Otherwise, parameter estimation is a major research area.

Searching parameter space



Problem: find global minimum of the cost function.

Need to:

- search space efficiently
- converge to a minimum
- avoid getting stuck in local minima

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Simulated Annealing

Metropolis *et al.* (1953). J Chem Phys 21: 1087.
Kirkpatrick *et al.* (1983). Science 220: 671.

1. Compute $E = E_{old}$ using parameters θ_i .
2. Change one of the values in θ_i (make a "move").
3. Compute $E = E_{new}$ using the newly generated set of θ_i .
4. If $E_{new} < E_{old}$, keep the new values of θ_i (accept the move).
5. If $E_{new} > E_{old}$, keep the new values of θ_i with Boltzmann probability $\exp(-\Delta E/T)$; otherwise restore the old values in θ_i (reject the move).
6. Repeat 1-5, making moves by changing each element of θ_i in turn, allowing T to decrease from its initial value to zero. High T allows large movements in parameter space.

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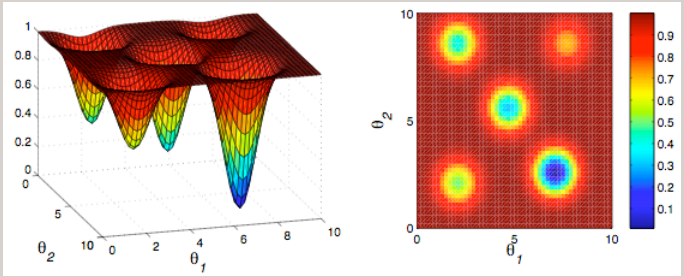
In general, need to combine:

1. ***Global search*** — avoid local minima; slow convergence
2. ***Local search*** — refine minima; fast convergence.



Simulated annealing does this by changing T. Gives good solutions, but is very slow.

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Evolutionary Algorithm Optimisation

Fomekong-Nanfack *et al.* (2007). *Bioinformatics* **23**, 3356–3363.

An alternative optimisation strategy is to use an ***evolutionary algorithm***:

- Treat a parameter set as the "genome" of an individual.
- Each individual has a "fitness" determined by a combination of the cost function and a penalty (to account for the 'feasibility' of the parameters.
- At each generation, rank individuals on fitness and select the fittest to seed the next generation (selection).
- 'Mutation' and 'recombination' (parameter changes) allow parameter space to be searched.

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Local Optimisation

1. Optimise locally to speed up convergence.
2. One option is to move using steepest descent of the cost function, but requires evaluation of the derivative. No analytical expression and costly to approximate.
3. Use downhill simplex (Nelder-Mead). Evaluate the cost function at n+1 points (for an n-dimensional parameter space). Treat each point as a vertex of a simplex. Move the worst point to search for local minima (with progressively smaller moves).
4. Improves goodness of fit and speed of convergence.

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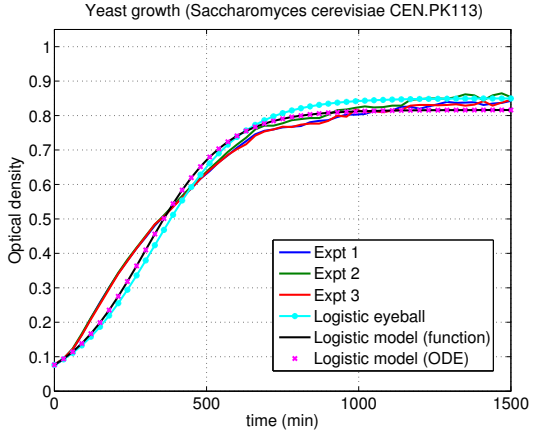
Logistic growth? $\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right)$

- Consider experimental data on the growth of yeast.
- Dynamics look a bit like logistic growth ...



- But logistic growth is too slow at first, and too fast later.

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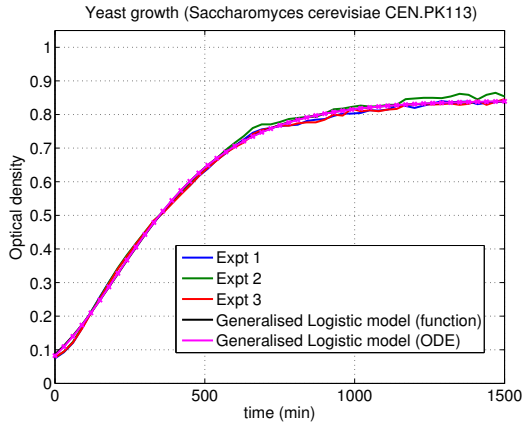
Generalised Logistic growth? $\frac{dx}{dt} = rx\left(1 - \left[\frac{x}{K}\right]^{v}\right)$

- Generalised logistic model gives a better fit, but the parameters are poorly constrained...



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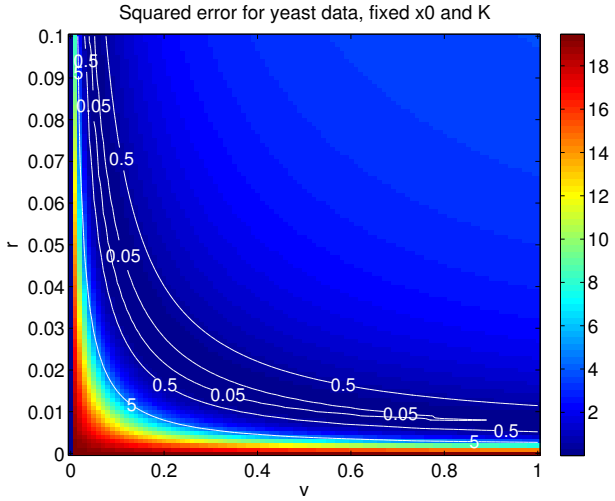
Generalised Logistic growth? $\frac{dx}{dt} = rx\left(1 - \left[\frac{x}{K}\right]^{v}\right)$

- error is small across a wide range of parameter space...



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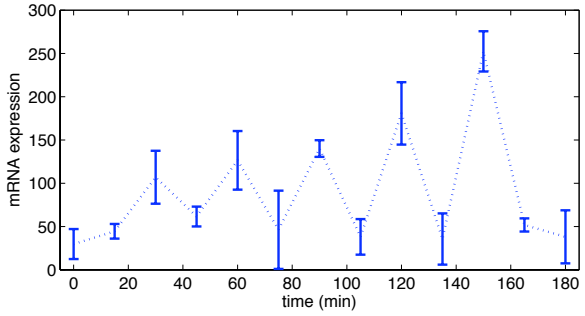
A harder problem

- mRNA expression levels following growth factor treatment of cultured cells
- five replicates (A–E) at 13 time points

time (min)	A	B	C	D	E
0	30.4577	24.2926	33.2472	34.0589	26.8882
15	47.6457	47.6369	41.5029	43.3276	42.5643
30	104.0833	108.6458	102.0752	115.9327	104.3348
45	61.8864	66.6506	61.6132	60.8385	57.1550
60	127.3598	119.2069	129.4594	134.0056	122.4289
75	50.9386	52.9187	38.6800	39.4438	49.5044
90	135.0155	140.4649	141.0930	140.5744	143.4661
105	41.0047	43.6159	31.6494	37.5628	36.8781
120	174.5059	183.8129	177.2440	189.6021	178.5009
135	40.6576	39.1105	33.4044	27.1605	37.7179
150	244.8919	253.0174	252.4838	258.4072	252.9015
165	50.0274	55.1471	48.1998	53.1479	53.0043
180	38.8440	37.2545	44.3188	29.4739	40.9847



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A harder problem

- ***Challenge***: Infer values of a and b for which the following model (a Bliss-Painter-Marr negative feedback model) best accounts for the data
- $x1$ represents the mRNA in question, $x2$ and $x3$ are proteins (unmeasured in the experiment)
- Know from other data that $k = 1$ and $100 \le a \le 300$ and $0.05 \le b \le 0.3$

$$\frac{dx_1}{dt} = \frac{a}{1+x_3} - bx_1$$

$$\frac{dx_2}{dt} = b(x_1 - x_2)$$

$$\frac{dx_3}{dt} = bx_2 - c\frac{x_3}{1+kx_3}$$

$$c = \begin{cases} 5, & t < 0 \\ 5 + 0.2t, & 0 \le t < 50 \\ 15, & t \ge 50 \end{cases}$$

- ***Method***: Solve the equations for different values of a and b and evaluate the squared error cost function specified earlier
- Use a search algorithm to search the allowed parameter values to identify the optimal values (lowest cost function value)

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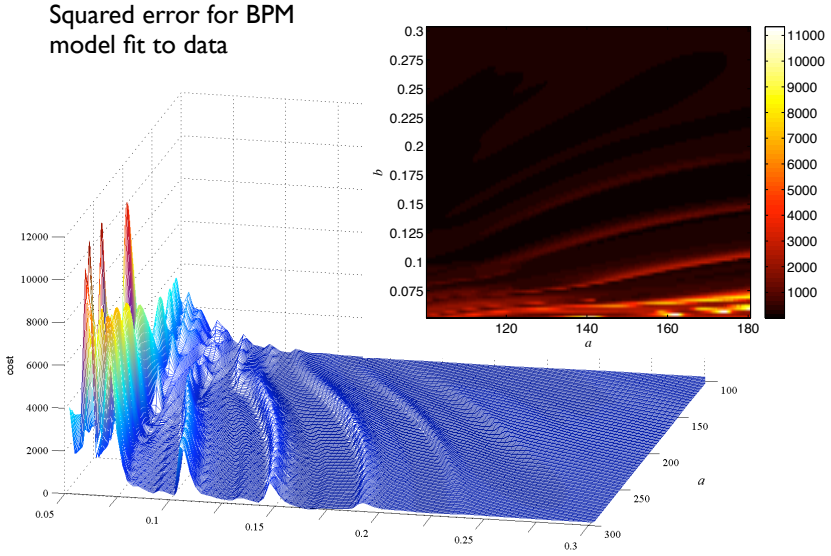
Fitness Landscape for BPM Model

Squared error for BPM model fit to data



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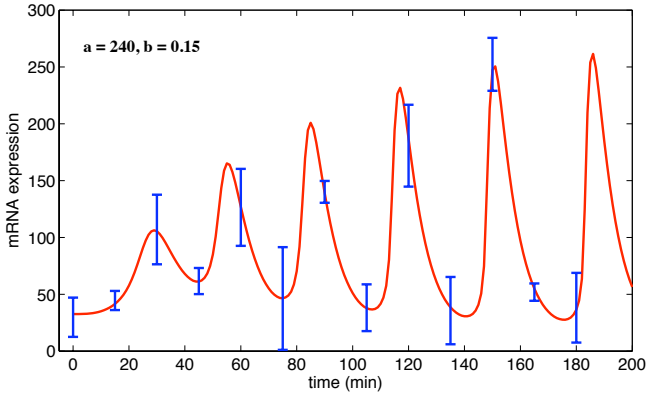
Best fit solution from Nelder-Mead search

cost = 0.2898



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Parameter sensitivity

If we have a solution of the ODE model

$$\frac{dx_i}{dt}(t) = f_i\left(\left\{x_{\langle i\rangle}(t)\right\}, \mathbf{p}_i\right); \quad x_i(0) = x_{i0}, i = 1,2,...,n$$

for a given set of parameters.

Question: How **sensitive** is this solution to changes in the parameters? Often most appropriate to think in terms of solution "features" (corresponding to biological function).

Given a feature ϕ, the sensitivity gain is defined as: $S_p^{\phi} = \frac{\delta\phi/\phi}{\delta p/p}$

(relative change in feature)/(relative change in parameter value)

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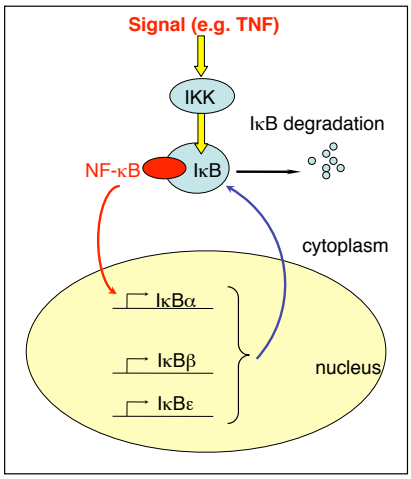
The NF-κB – IκB oscillatory feedback loop



- Central mediator of inflammatory response.
- NF-κB is a transcription factor.
- Normally held in the cytoplasm in a complex with IκB proteins.
- Inflammatory signals activate IKK, which induces the degradation of the IκB proteins — releasing NF-κB, which enters the nucleus and regulates transcription.
- Negative feedback via IκBα results in oscillations.

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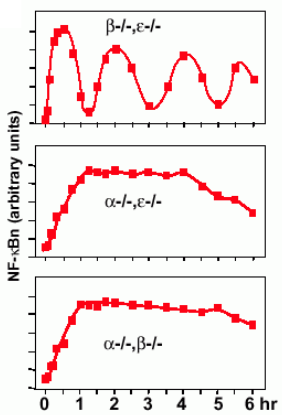
The NF-κB – IκB oscillatory feedback loop

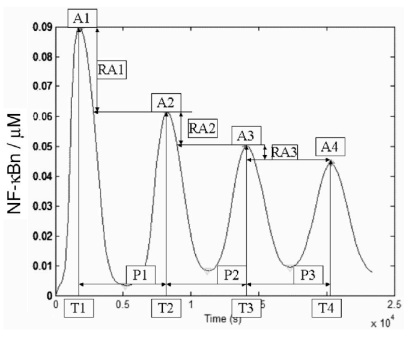
Experimental data (nuclear NF-κB)



Hoffmann *et al., Science* **298**, 1241–1245 (2002).
Nelson *et al., Science* **306**, 704–708 (2004).

Summary features:

- Peak timings Ti (oscillatory period Pi)
- Peak amplitudes (Ai)



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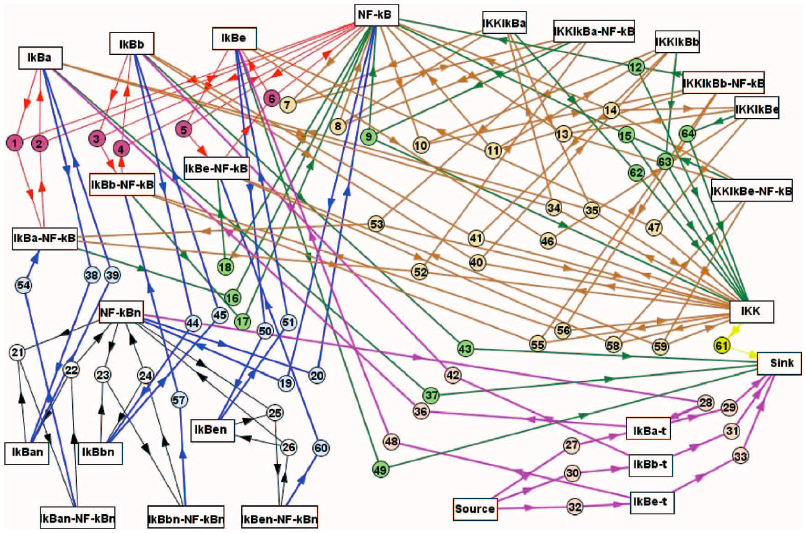
NF-κB Model Network Diagram



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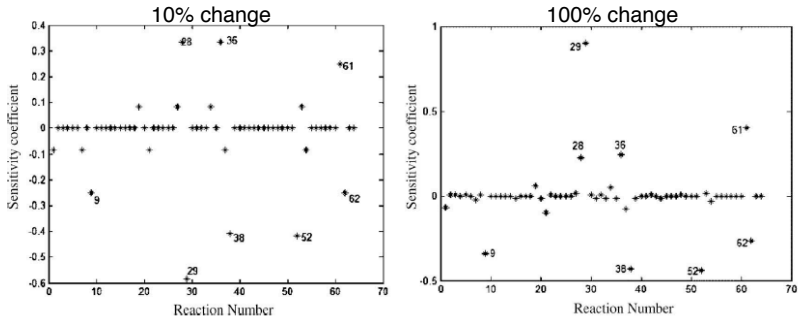
Parameter Sensitivity (T3)

- Construct ODE model representing the interaction network (26 variables, 64 parameters)
- Find parameters that reproduce observed oscillations
- Assess parameter sensitivity of features: $S_p^{\phi} = \dfrac{\delta\phi/\phi}{\delta p/p}$



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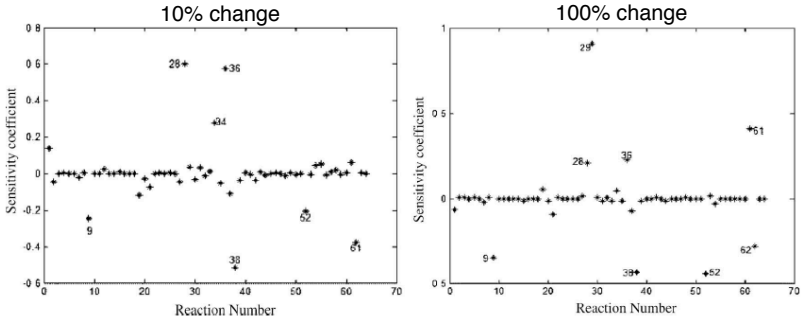

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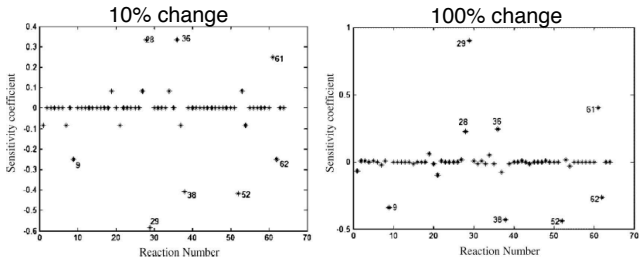
Parameter Sensitivity



- Only 9 out of 64 parameters have a significant impact when altered by 10% (ISI > 0.2). The same parameters were significant for other features.
- The most significant parameters are different for larger parameter changes (100%), due to model nonlinearity.
- All 9 parameters refer to reactions involving only free IKK and IκBα — suggesting that model reduction might be possible.

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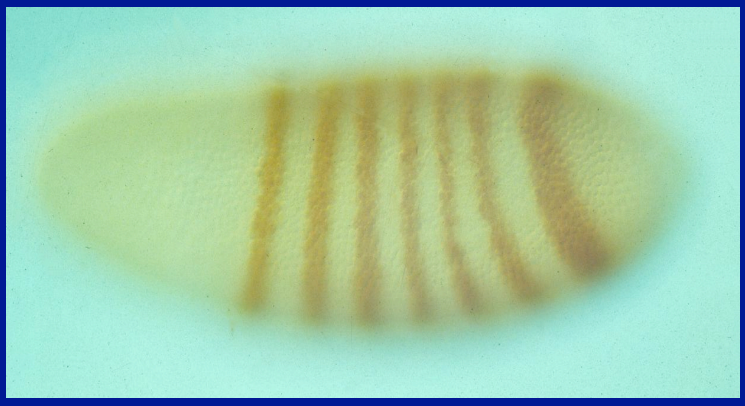
Segmental gene expression in the *Drosophila* embryo: pair-rule stripes



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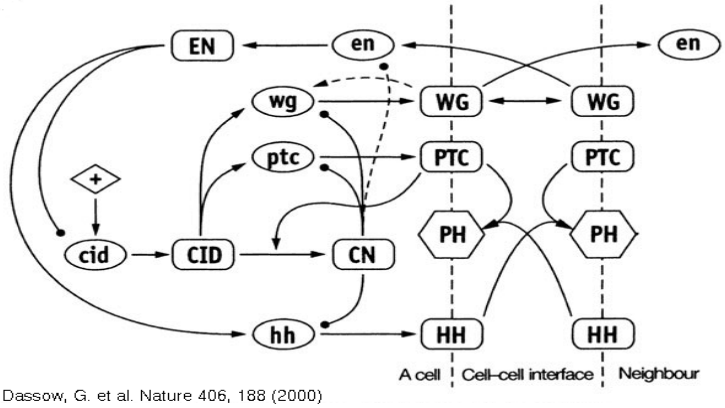
The segment polarity network

- A spatially distributed network, involving signalling between neighbouring cells.
- Ovals = mRNAs, rectangles = proteins, hexagons = protein complexes.



von Dassow, G. et al. Nature 406, 188 (2000)

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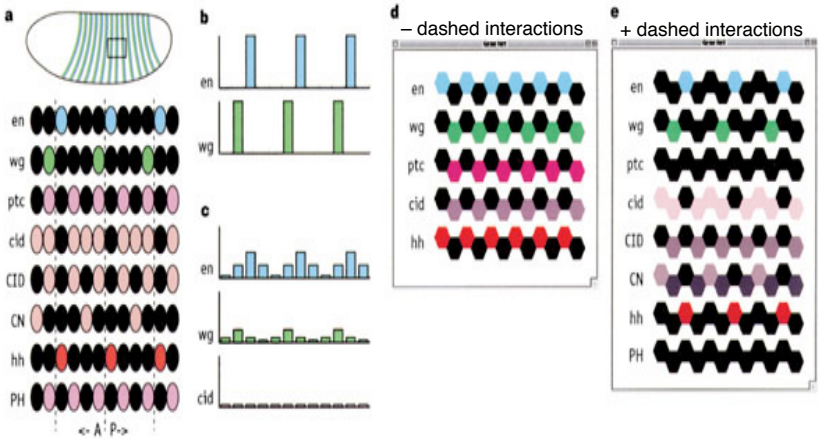
Segment polarity gene expression

- Characteristic expression pattern has a 4-cell periodicity (a).
- 'Crisp' (b) and 'Degraded' (c) initial conditions.



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ODE Model: parameter search

- The model has 12 variables per cell and 48 parameters. Parameter values are unknown and no quantitative data are available for inference.
- Perform random searches of parameter space: Given the (experimentally-established) network topology and initial conditions, for which parameter sets does a suitable stable pattern emerge?
- 1,192 'solutions' out of 240,000 sets (1/200).
- On average, a random choice of parameter has a 90% chance of being compatible with the desired behaviour ($0.9^{48} \sim 1/200$).

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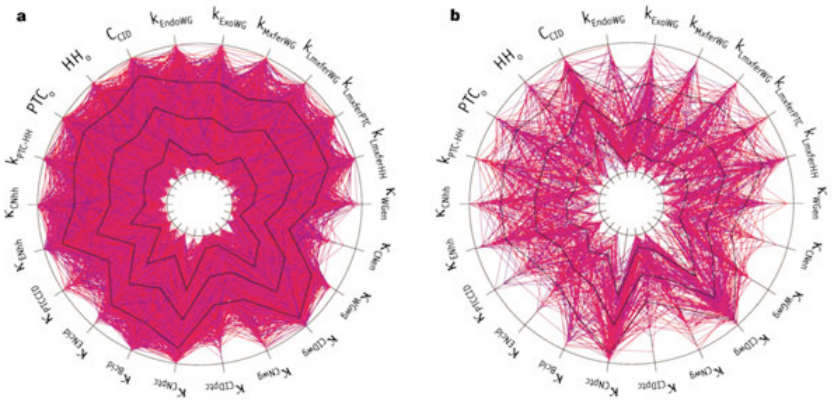
Maps of appropriate parameters

- Red = highest score; blue = barely meet expression criteria.
- Each 'spoke' is the log-scale axis for that parameter.



"sharp" initial data

"degraded" initial data

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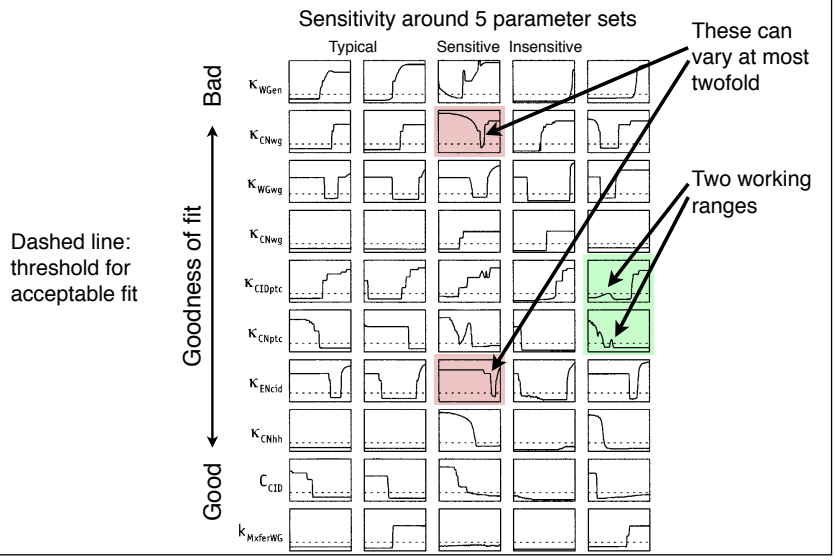
Local parameter sensitivity



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Robustness and modularity of the network

- The desired steady state expression pattern is observed very frequently in the random parameter search.
- Most parameters can range over several orders of magnitude.
- Local sensitivity analysis: most parameters can vary at least 10-fold from base values.
- The desired behaviour is observed frequently using 'degraded' initial stimuli.
- The behaviour is stable if additional complexity is added: the core topology is robust.
- This behaviour is resistant to variation in the kinetic parameters.
- The network is a *minimal module*: the desired behaviour cannot be recovered in a sub-network.
- The network exhibits other behaviours robustly.

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Discussion

- Parameter estimation is a challenging research area.
- There may not be a unique best fit.
- The more data the better (as long as it is good quality). (Modellers will ALWAYS ask for more data!!!)
- Parameter sensitivity characterises how solution features vary with parameters.
- Sensitivity is intimately linked to estimation - if a feature is sensitive to parameter variation, it is more likely to be constrained by available data.
- **Next practical:** COPASI for parameter estimation ~~& sensitivity analysis~~ (but you can do this in COPASI...)

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