Black boxes and black bags

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Biological systems as networks

- Molecular biology considers biological systems as sums of linear combinations of parts
- ... clearly does not work
- So consider biological systems as networks of components.
- Here as a recursive network of failure-prone elements - don’t care what the elements are.

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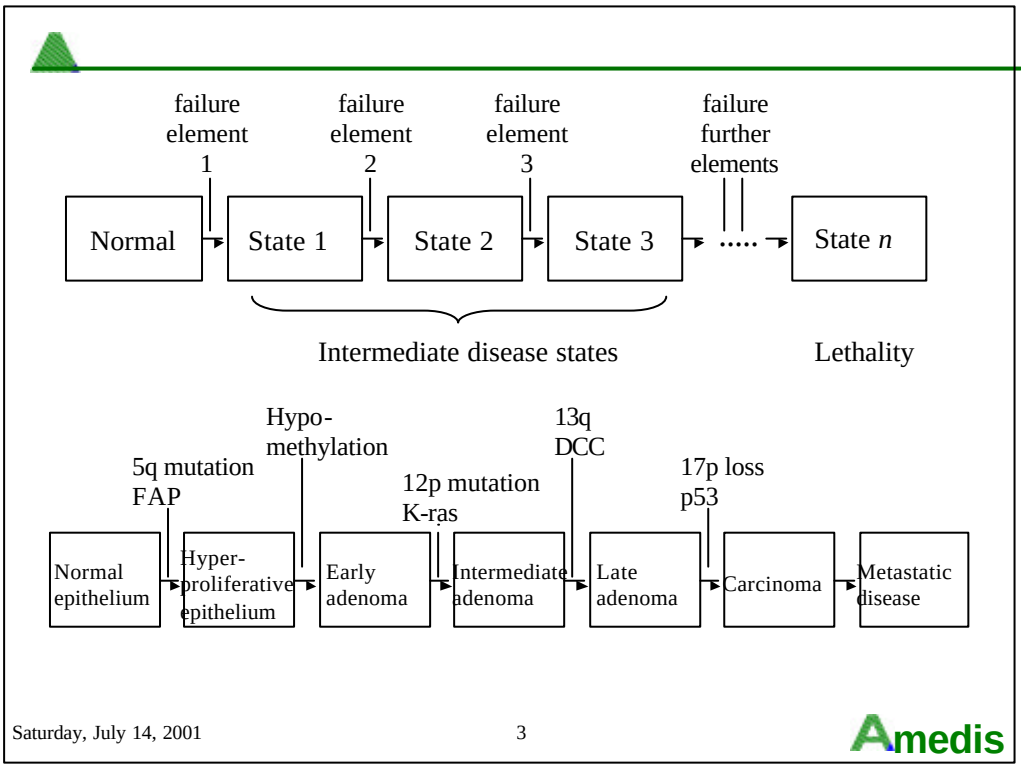
failure element 1
failure element 2
failure element 3
failure further elements
Normal
State 1
State 2
State 3
.....
State n
Intermediate disease states
Lethality
5q mutation FAP
Hypo-methylation
12p mutation K-ras
13q DCC
17p loss p53
Normal epithelium
Hyper-proliferative epithelium
Early adenoma
Intermediate adenoma
Late adenoma
Carcinoma
Metastatic disease
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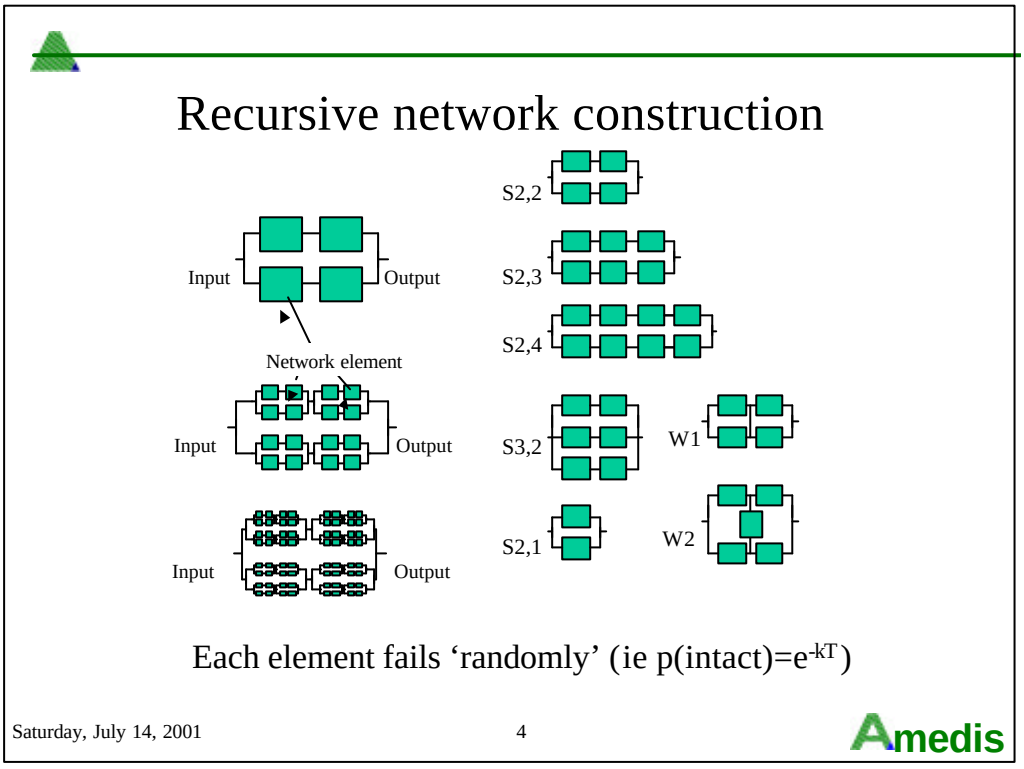
Recursive network construction
Input
Output
Network element
S2,2
S2,3
S2,4
S3,2
S2,1
W1
W2
Each element fails 'randomly' (ie p(intact)=e-kT)
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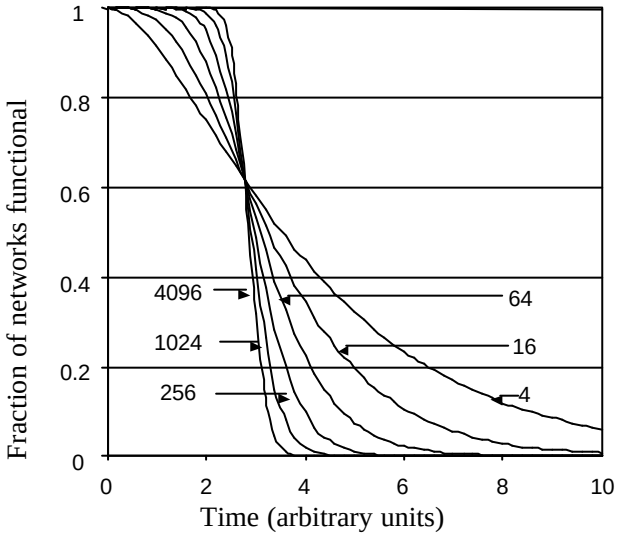
Increasingly large networks fail with increasingly exact timing



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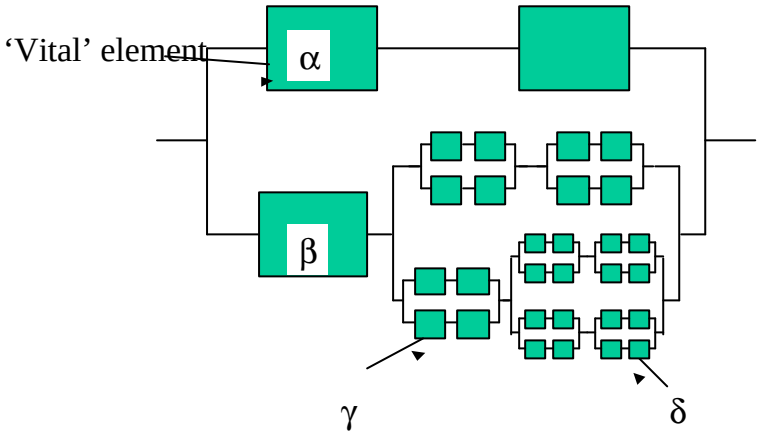
Asymmetric networks are constructed similarly



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Elements explain non-Gompertzian ageing

- 'Gompertz Law' - exponential increase in mortality rate with age.
- Very widely adhered to for 'normal' ages
- Deviation at extreme age in humans, fruit flies, probably others
- Is this due to an 'age-resistant' sub-population (ie the genetically super-fit)?
- No - is an outcome of a completely homogenous population of networks failing

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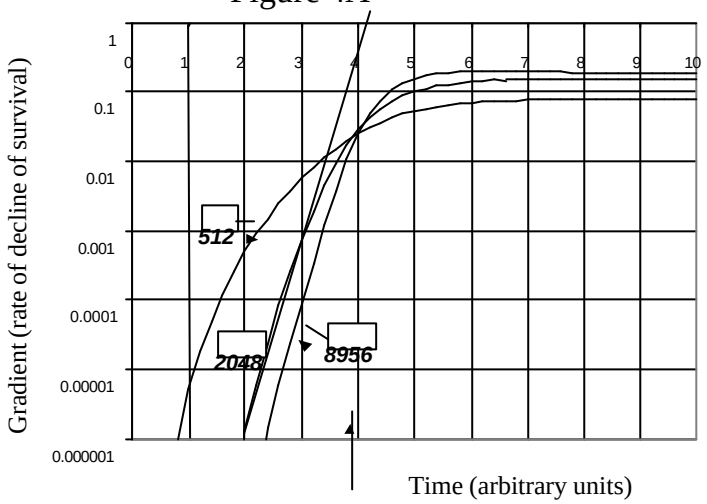
Figure 4A



Deflection point ≃ 90 years on human ageing scale

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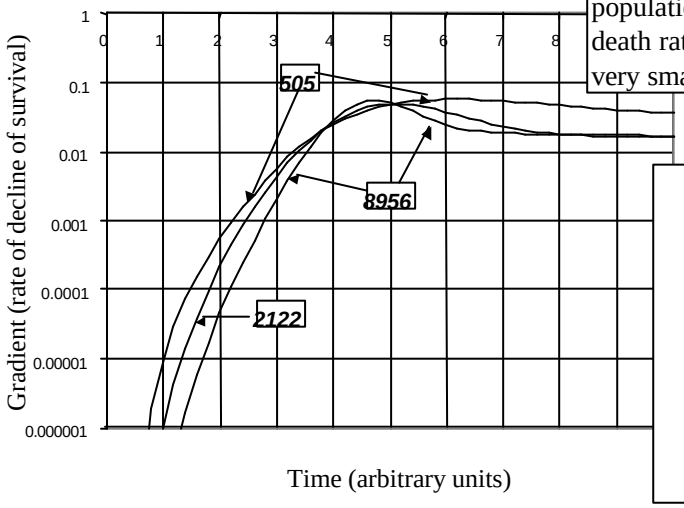
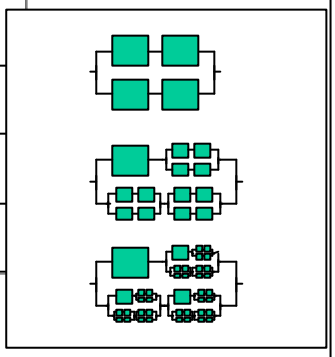
Asymmetric networks give even more extreme results

Observed for human populations: death rate at 100 < death rate at 90 (But - numbers very small)





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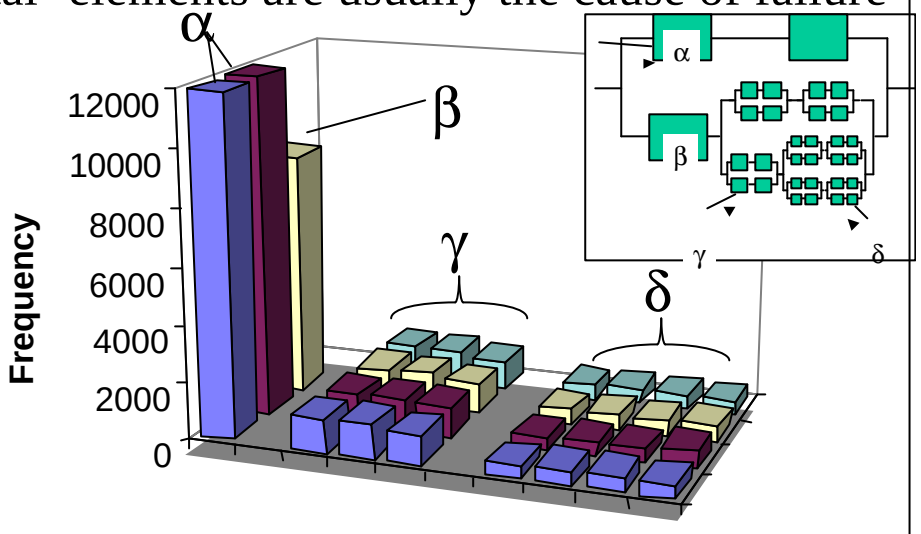
'Vital' elements are usually the cause of failure



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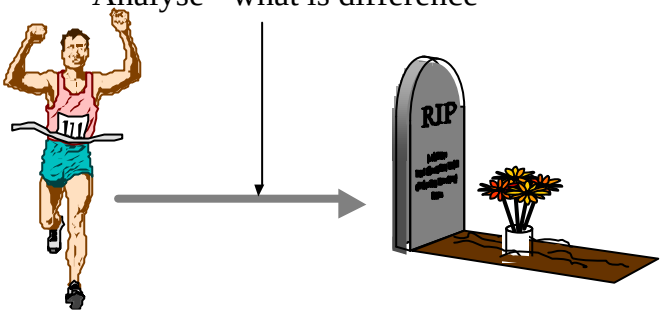
but what do we mean by ‘cause’

- Usually determined thus:

Analyse - what is difference



Healthy individual Ill / dead individual

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Variability of biology means we focus on *last* common change:

Analyse - what is difference

Many individuals - changing with time

‘critical’ change

Ill / dead individual

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‘Vital’ elements are usually the cause of failure

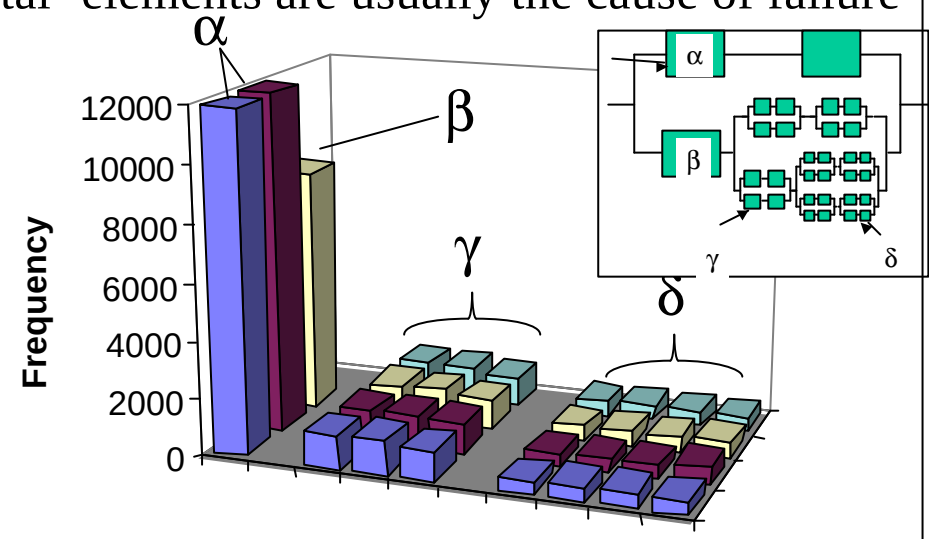

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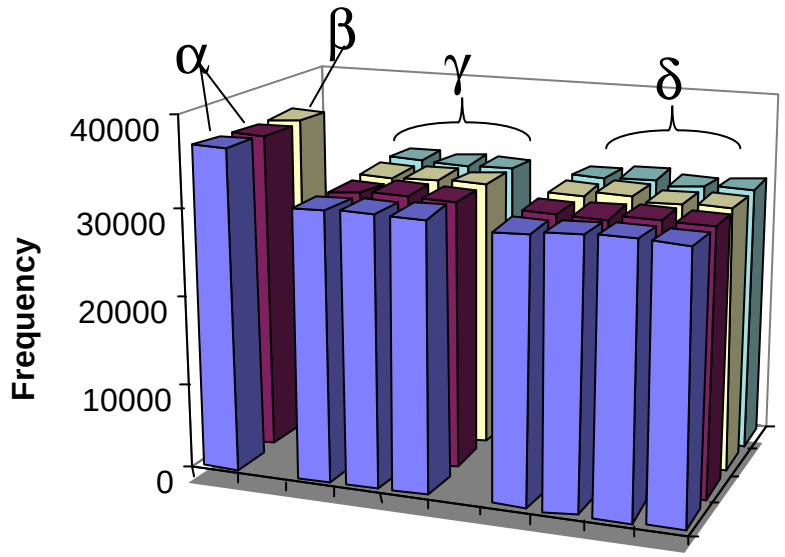
Figure 3B

Frequency with which element X *had failed* at network failure



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Parallels with oncogenes

- A small number of oncogenes are ‘the cause’ of cancer, ie
  - commonly found to be mutated in cancer
  - not mutated in non-cancer tissue
- but
  - on their own they cannot cause cancer
  - lots of other genes are mutated too

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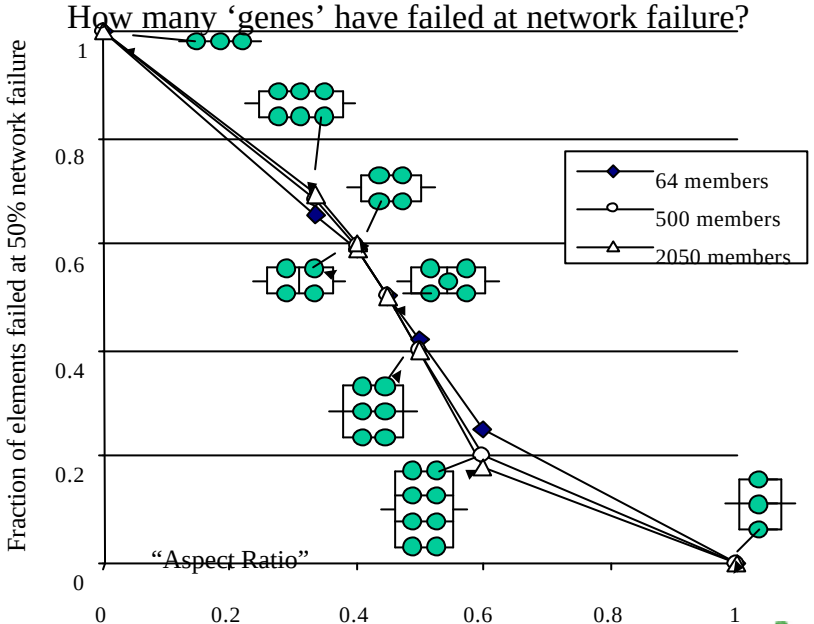
How many ‘genes’ have failed at network failure?



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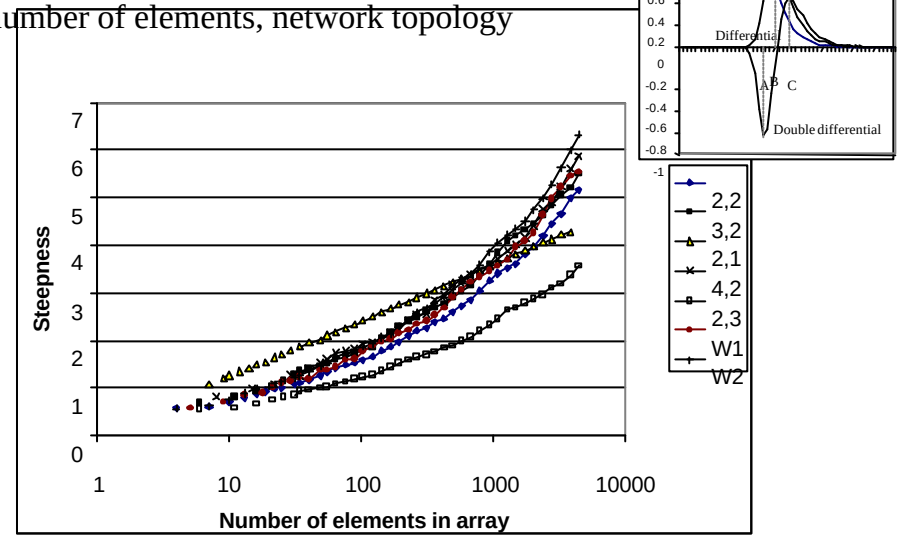
Implications for cancer treatment

- Targeting the ‘vital genes’ alone is not going to work
- For cancer vaccine approaches, whole cell (ie ‘minor gene’ approaches are at least as likely to work as oncogene antigen approaches

‘Steepness’ of failure curve depends on number of elements, network topology



Here's another odd thing ...

- Depending on network topology ...
- 'Vital' elements either are more commonly the 'cause' of early or late network failure:

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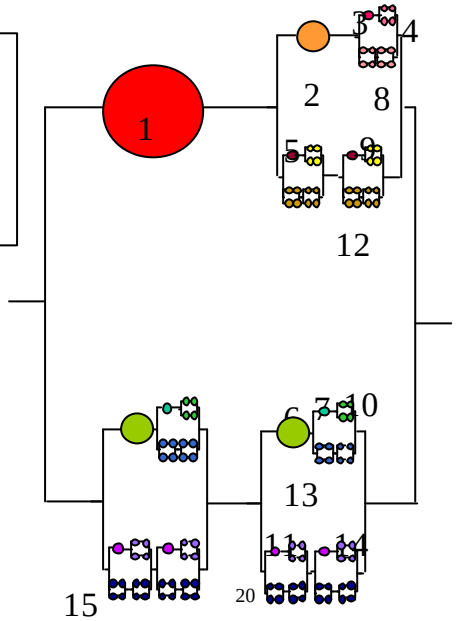
Tracking failure in asymmetric networks

Different 'types' of element (ie in different context - failure half-time is identical)



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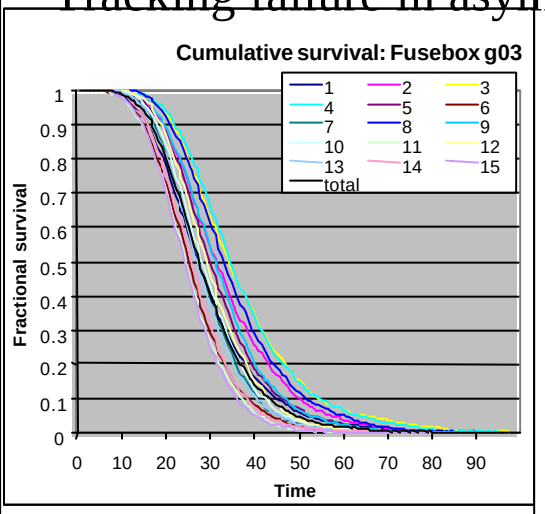
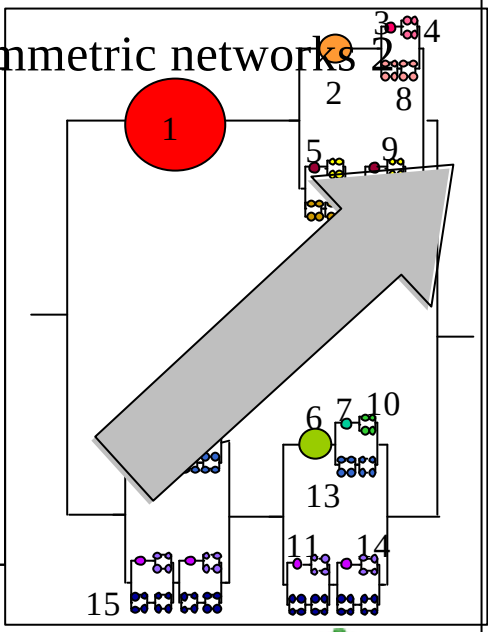
Tracking failure in asymmetric networks





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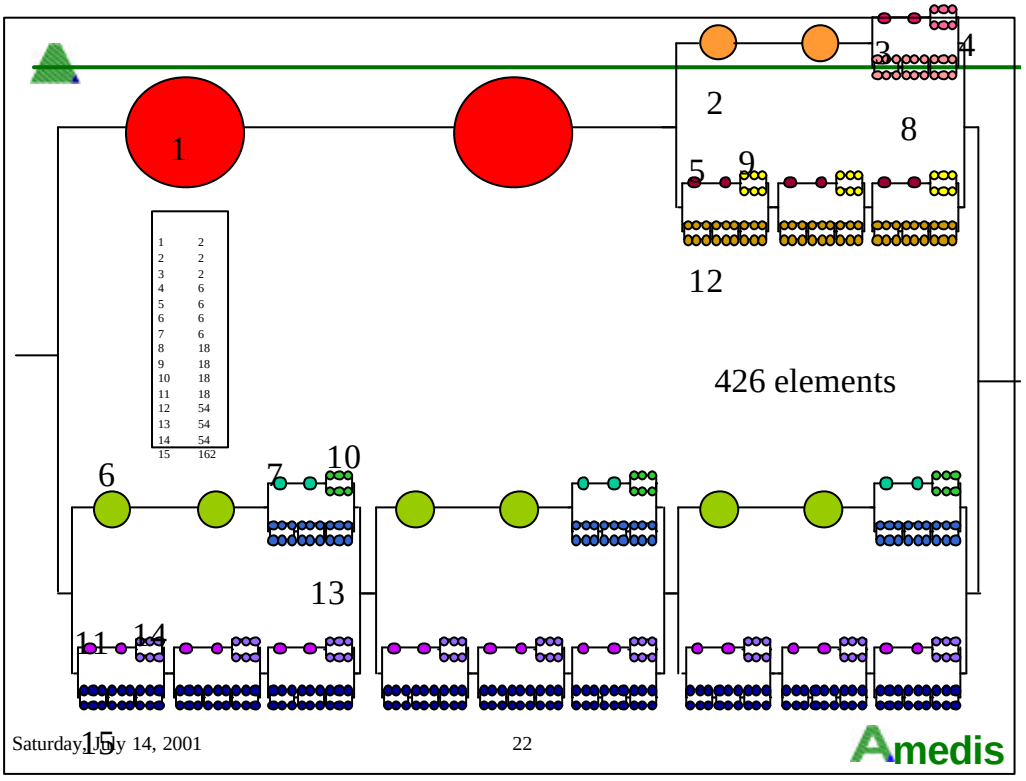

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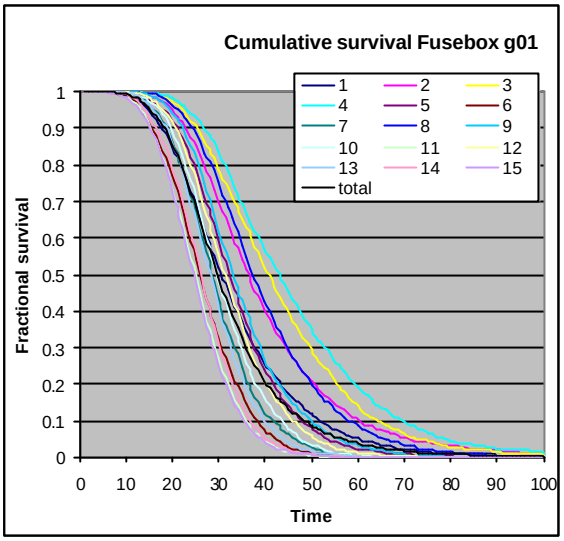

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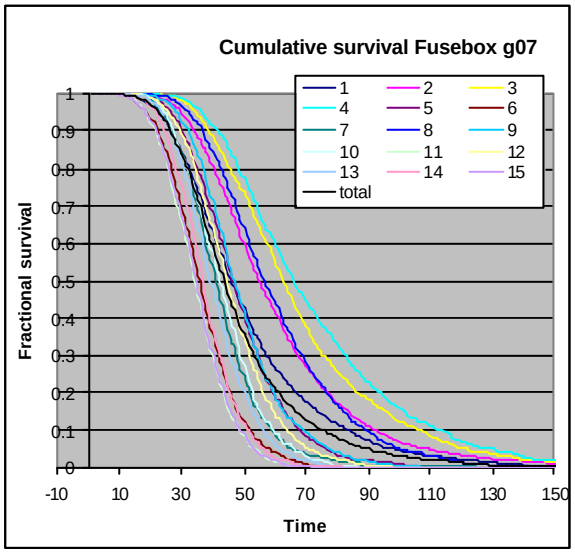

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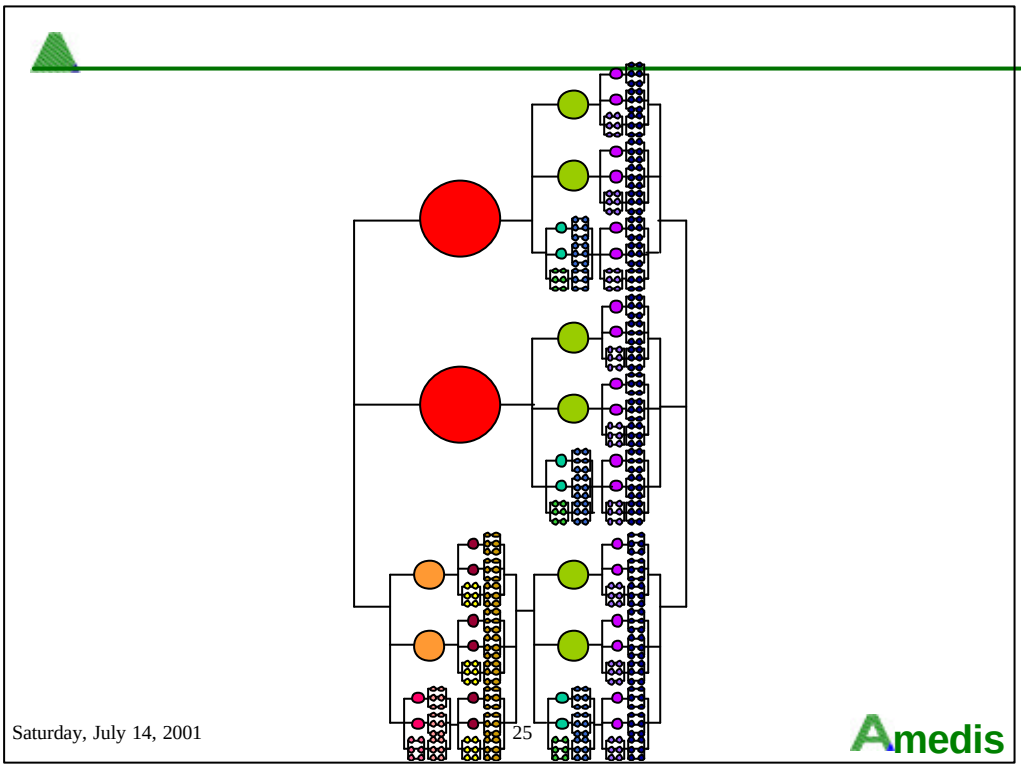

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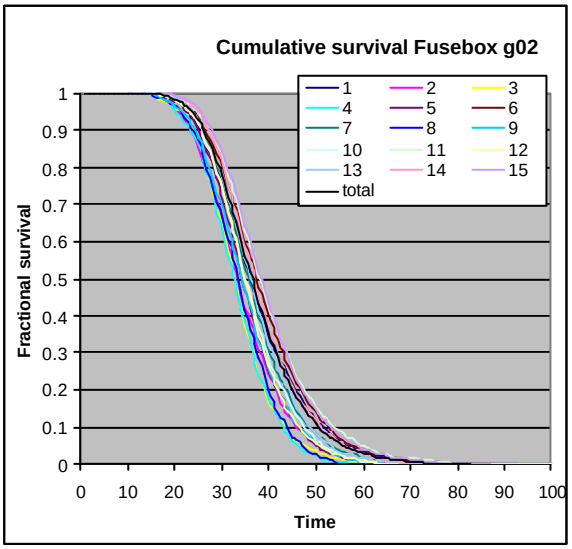

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Prognosis

- Useful to predict what sort of ‘genes’ are useful for
  - prognosis
  - therapy
- for cancers at different ages
- ... but presupposes you know the network topology

Why is biology so complicated?

- Thermodynamic argument:

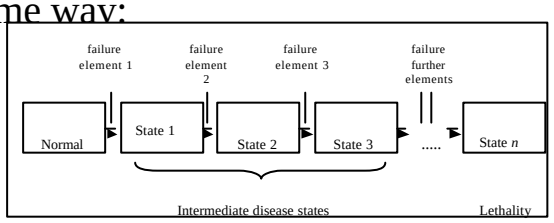
  (stand by - sums coming up)

$$F = k.\frac{K_a.C_a}{\sum_{1-n} K_n.C_n}$$

- Failure rate for a process dependent on rate of incorporation of the correct substrate (a) vs rate of all the incorrect ones (n)
  - Which is dependent on the free energy expended to incorporate correct and incorrect substrates

$$\Delta G = -RTL_nK$$

- If we have a linear series of ‘failing things’, all of which fail in the same way:



$$S = \text{survival after time } t = 1 - \prod_{1-n} (1 - e^{-F_n t})$$

For all the n elements in the series

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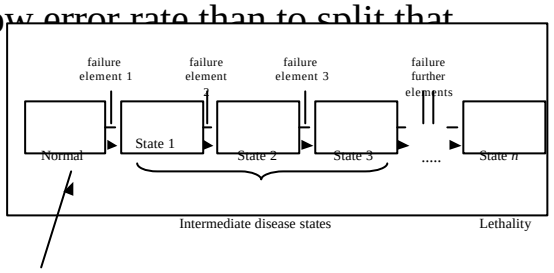
I think this means ...

- It is more efficient to use a given amount of energy to make sure that one of the elements in a linear series has a low error rate than to split that energy among two.



- Any chain of this sort

  will therefore be evolutionarily selected against on energetic grounds

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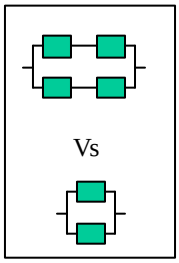
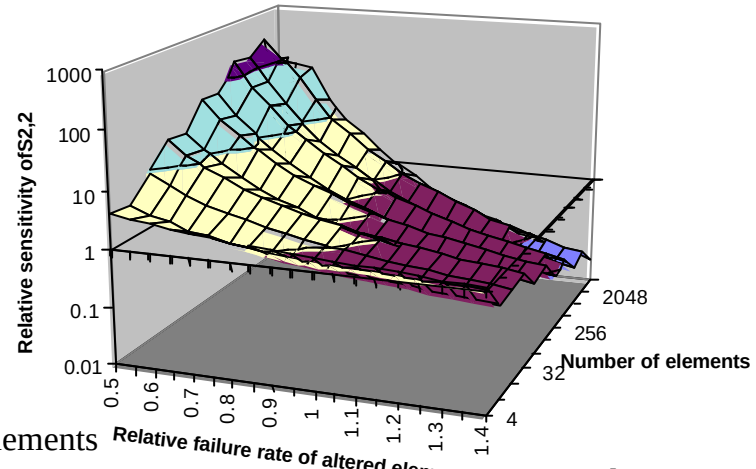
Model the sensitivity of a network to changes in elements





'better' elements 'poorer' elements

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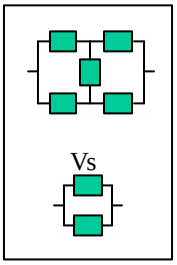
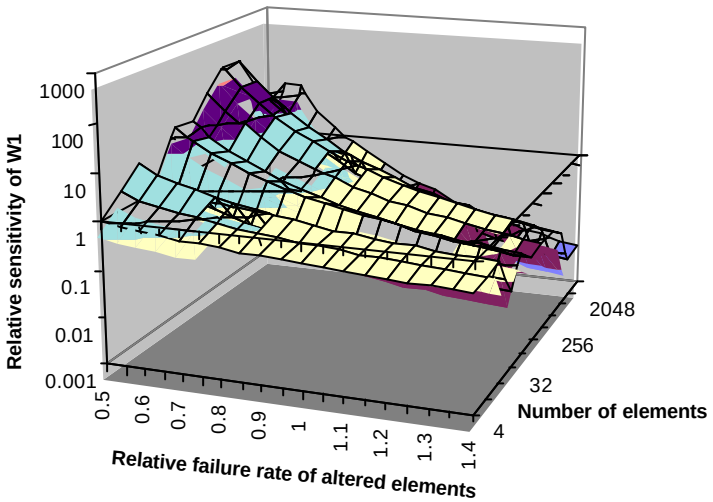
Figure 7B





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Conclusions

- I can model some of the aspects of age-related disease, some of them unexpected, *without* reference to the molecular mechanisms.
- This sort of structure makes evolutionary sense
- As suspected, the properties of biological systems owe as much to the structure of those systems as the components.
- But ... so what?