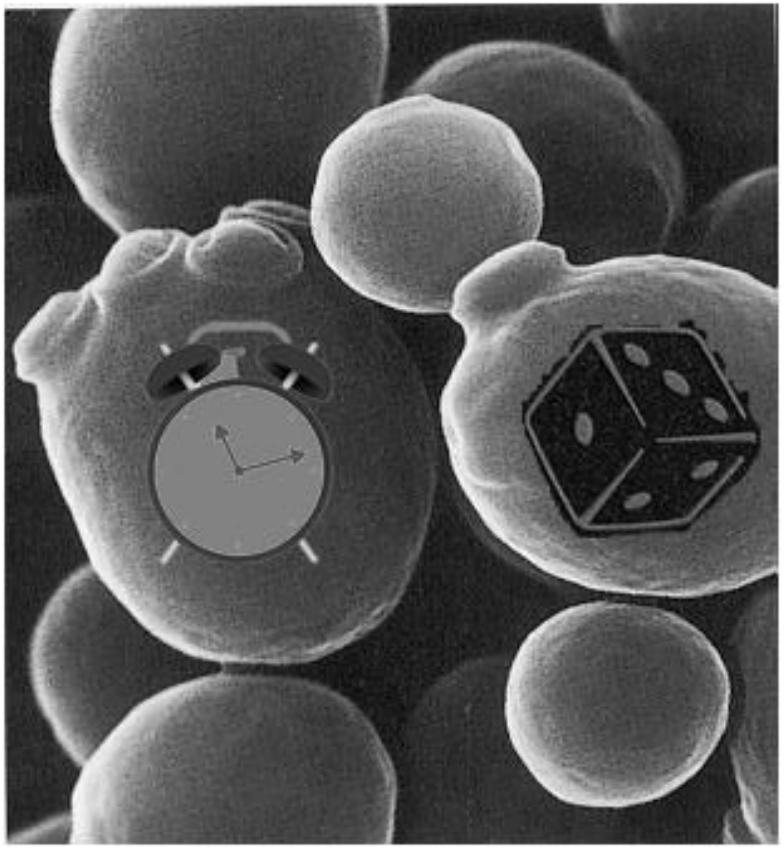
Modelling the Genome-wide Replication Program of Budding Yeast:
Timing from Stochasticity



Scott Yang
Nick Rhind (UMass Med)
John Bechhoefer (SFU)

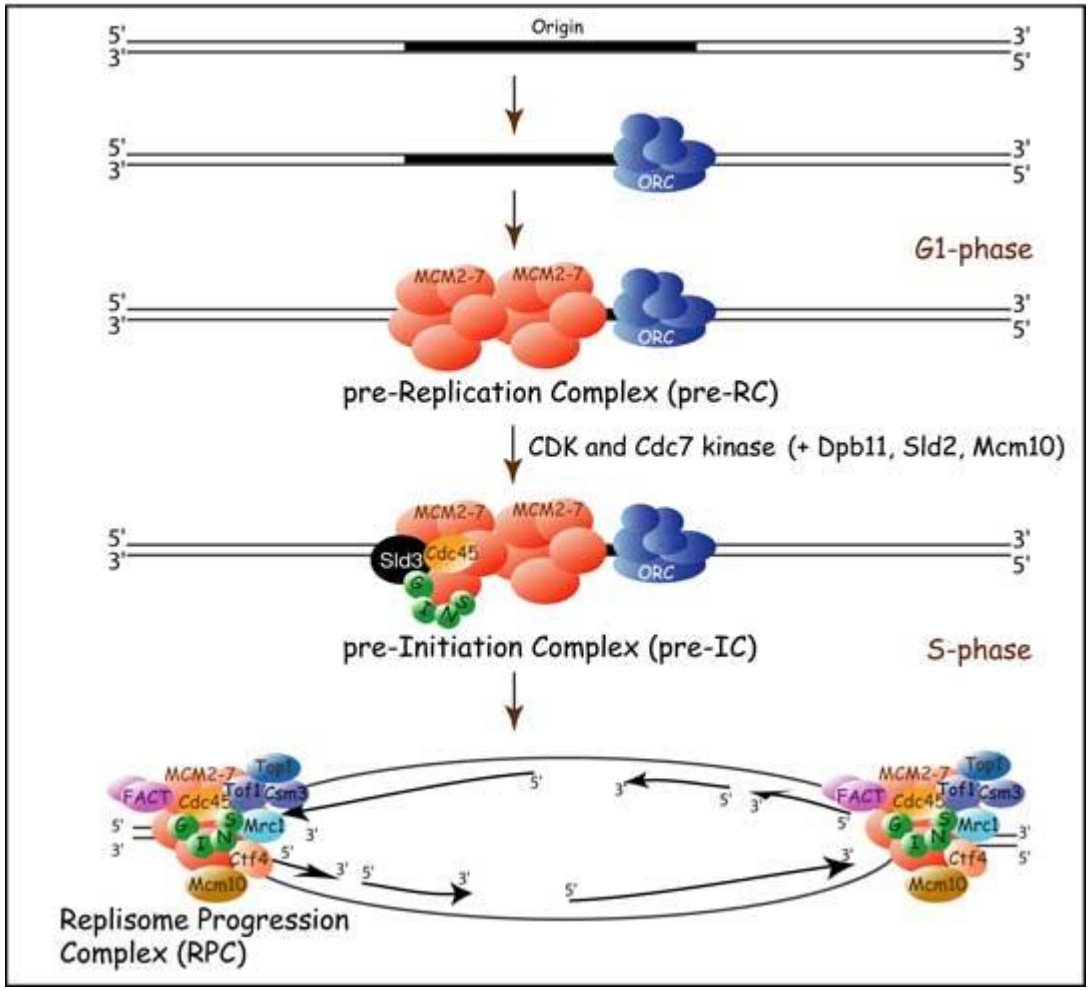
CMMT TGIF Series
Dec 17, 2010

Take-home messages

- Should consider DNA replication from a stochastic point of view

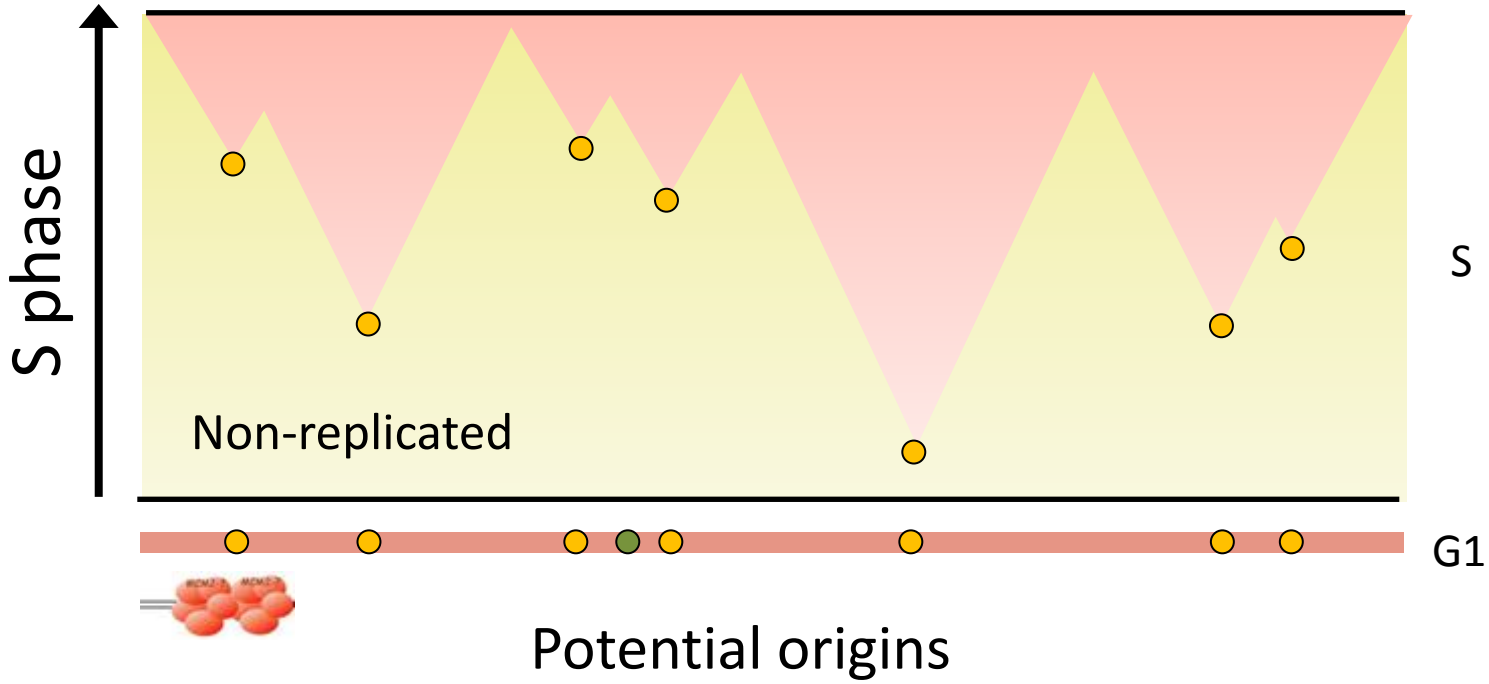
- Precise timing of the replication program can emerge from stochasticity

DNA replication



http://www.paterson.man.ac.uk/cellcycle/replication.stm

DNA replication: the Kinetics



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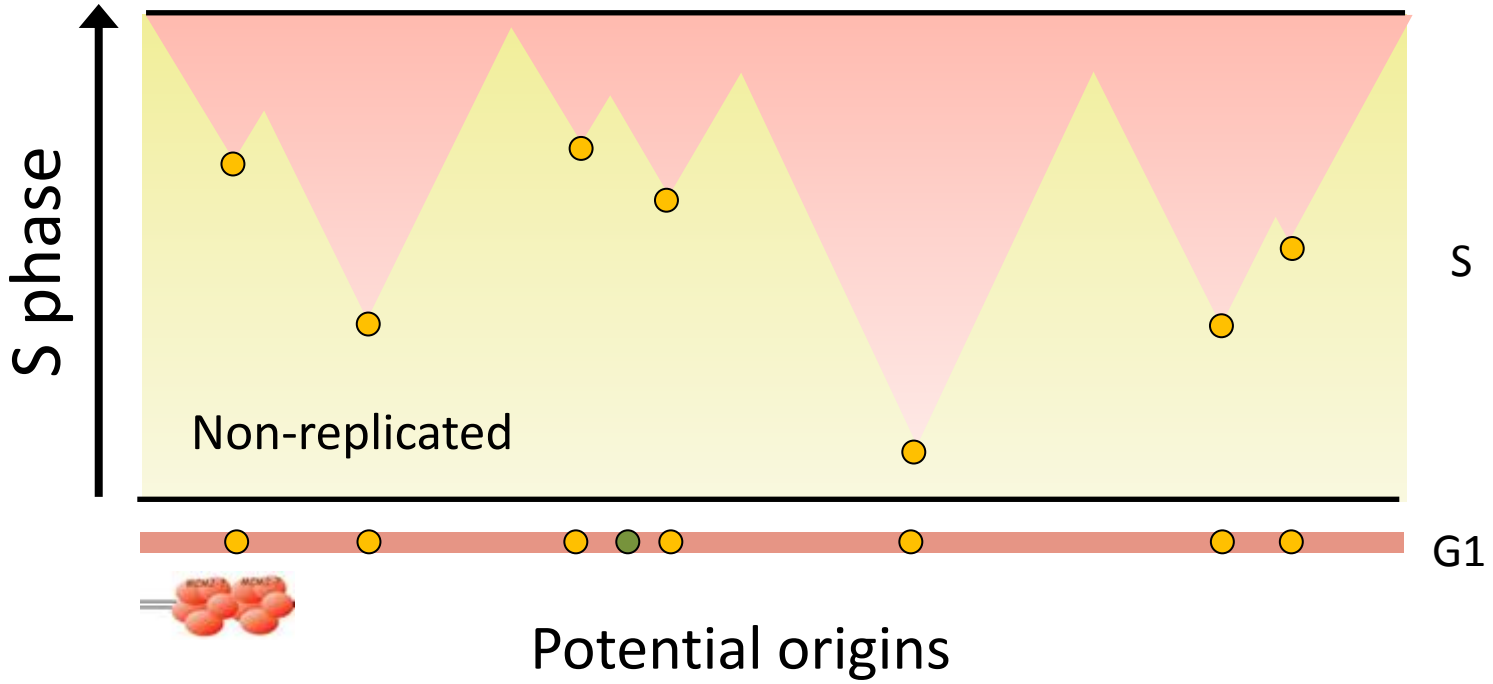
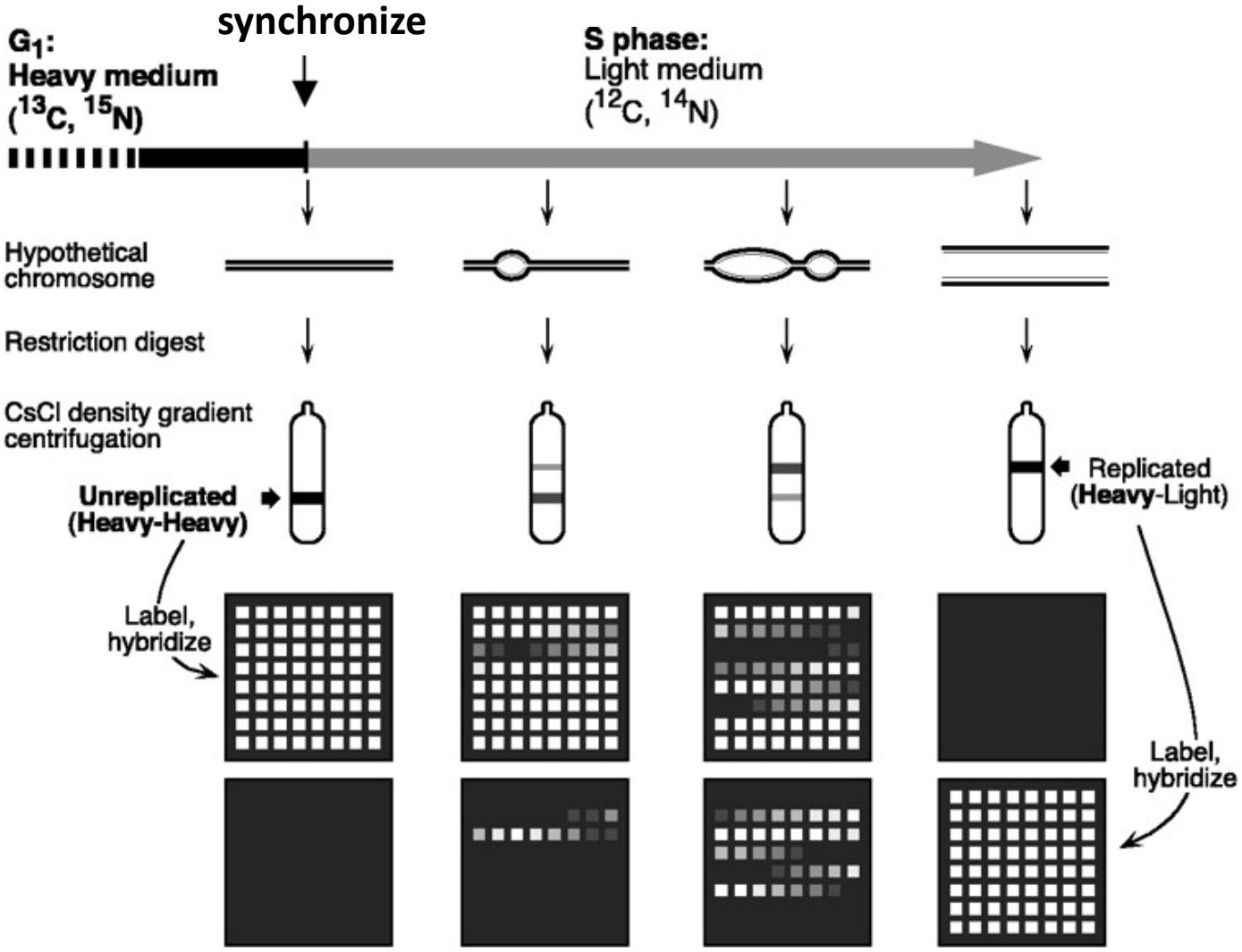


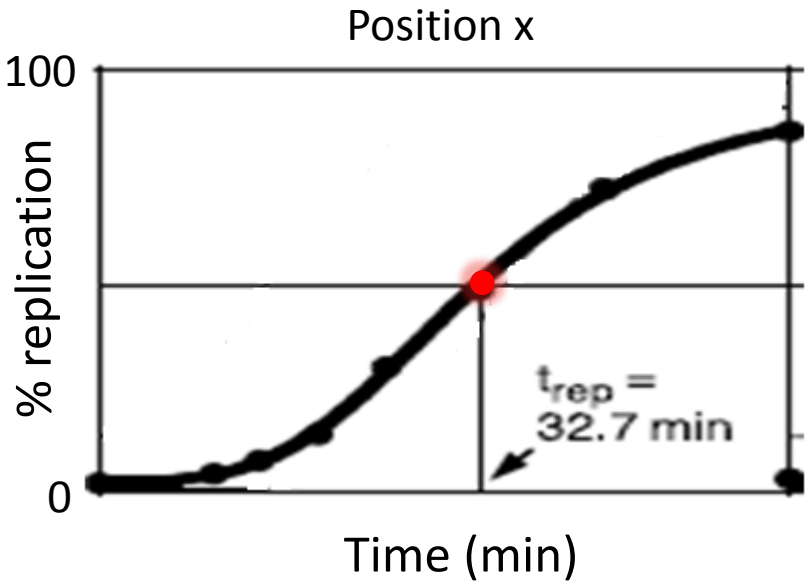
Origins + forks = replication program

A Microarray Experiment



Raghuraman et al. *Science* 2001

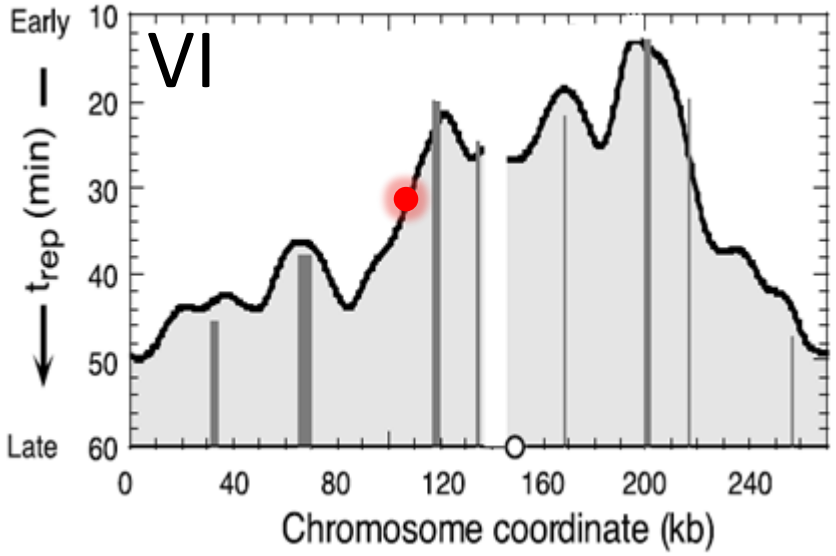
Replication profiles



Raghuraman et al. *Science* 2001

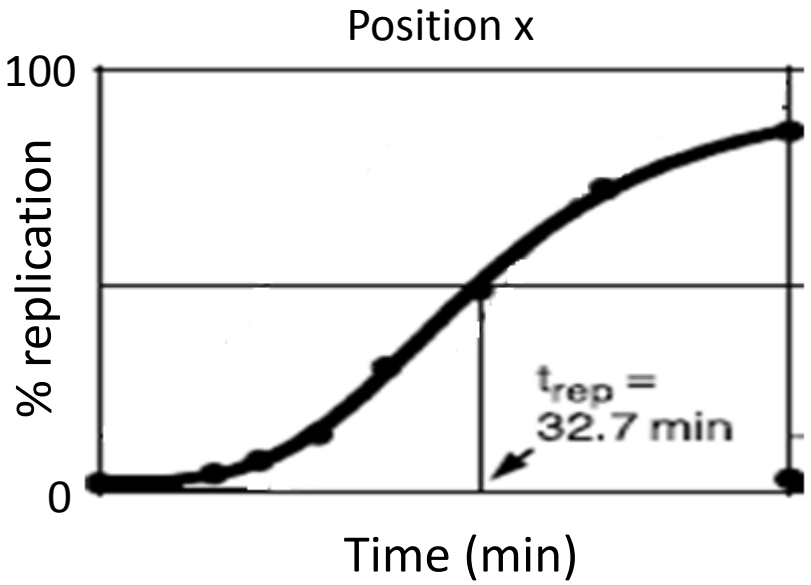
Replication profiles

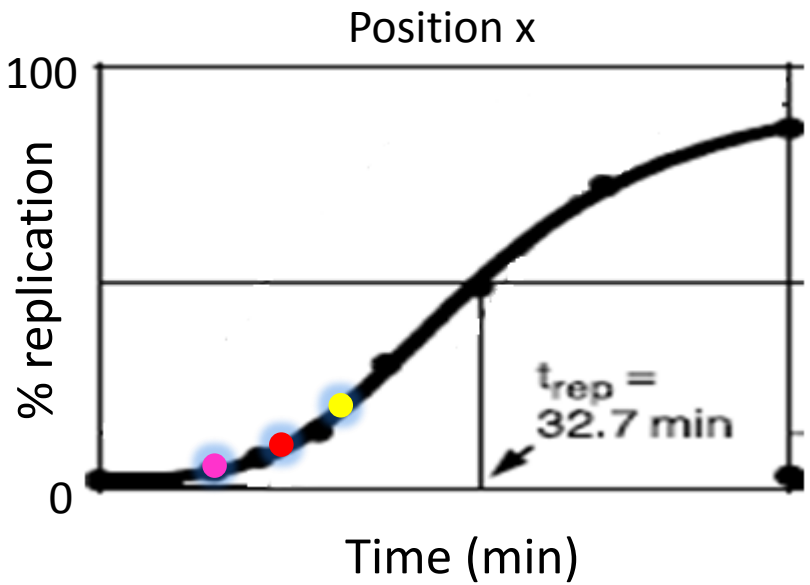
Replication time profile



Raghuraman et al. *Science* 2001

Replication profiles

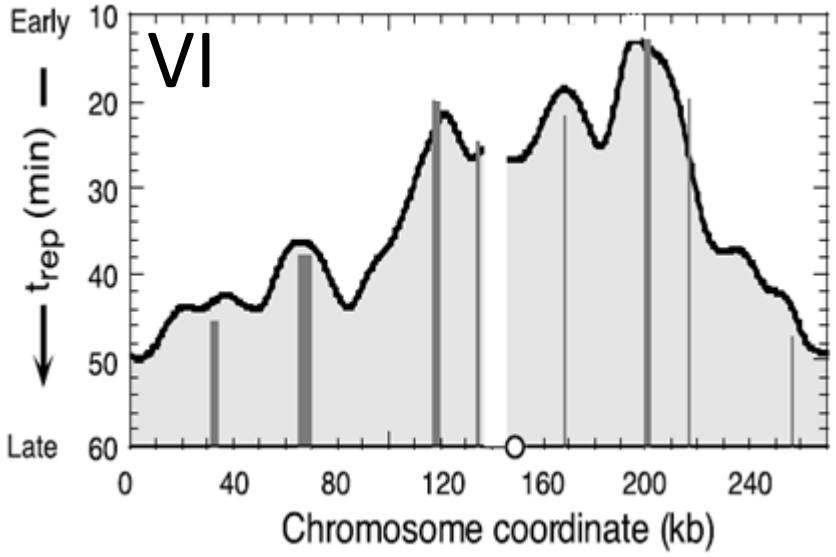




Raghuraman et al. *Science* 2001

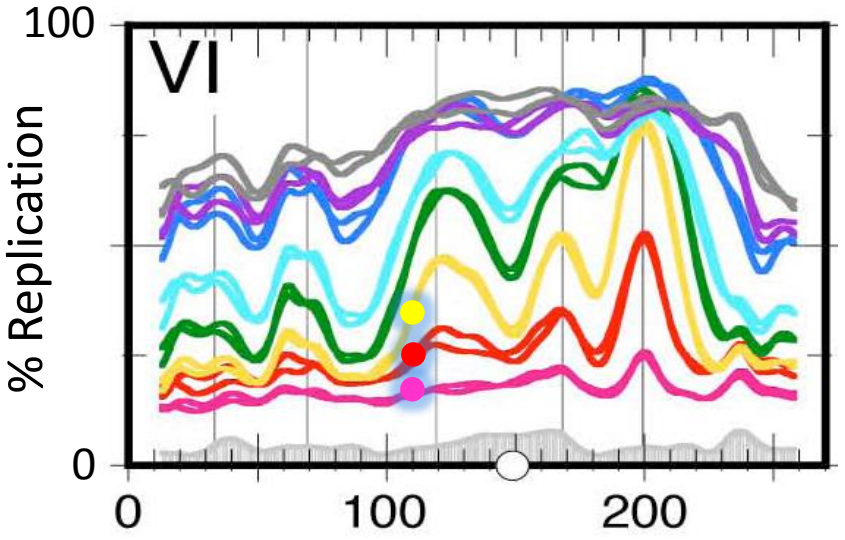
Replication profiles

Replication time profile



Raghuraman et al. *Science* 2001

Replication fraction profile



McCune et al. *Genetics* 2008

Point of Views

More deterministic

- Each origin has a preprogrammed firing time

- plus some variation around that time

Point of Views

More deterministic

- Each origin has a preprogrammed firing time
- plus some variation around that time

More stochastic

- Each origin has a distribution of firing times
- has an expected firing time

Point of Views

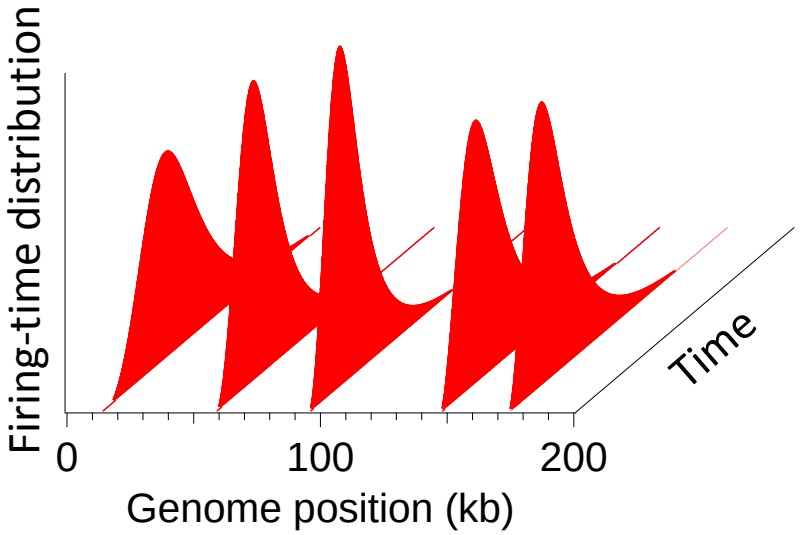
More deterministic

- Each origin has a preprogrammed firing time
- plus some variation around that time
- What counts the time and how?

More stochastic

- Each origin has a distribution of firing times
- has an expected firing time
- How to ensure precise firing time if needed?

Parametric model



x: origin position

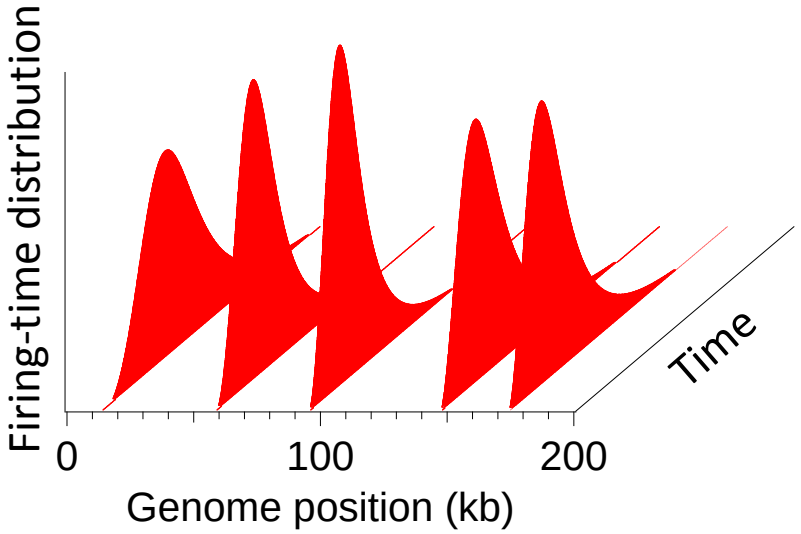
$t_{1/2}$: median of distribution

t_w: width of distribution

} Cumulative firing-time distribution = sigmoid function

v: globally constant fork velocity

Parametric model



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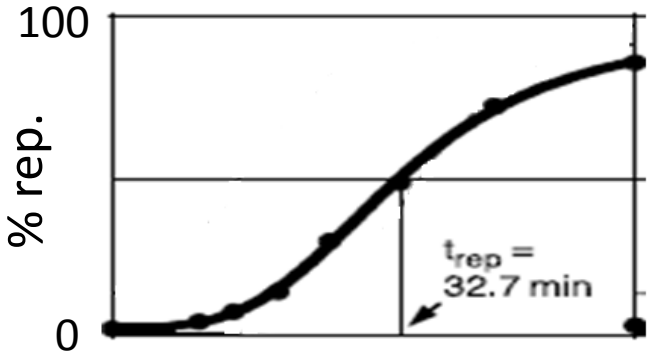
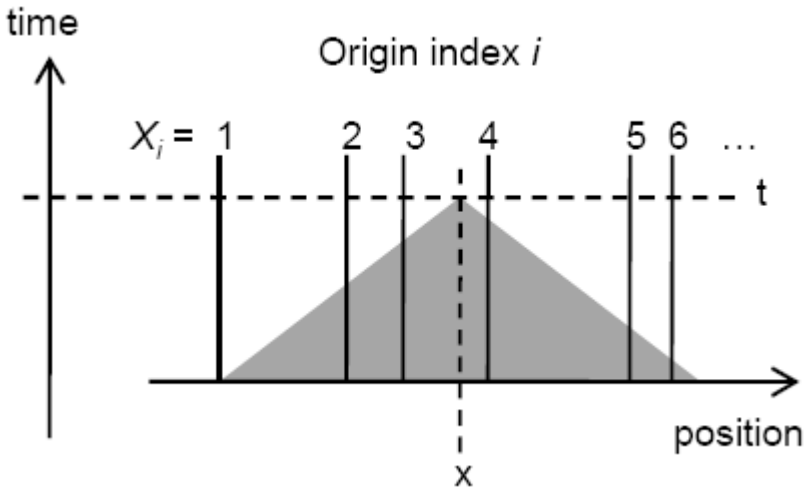


v: globally constant fork velocity

Key theoretical idea

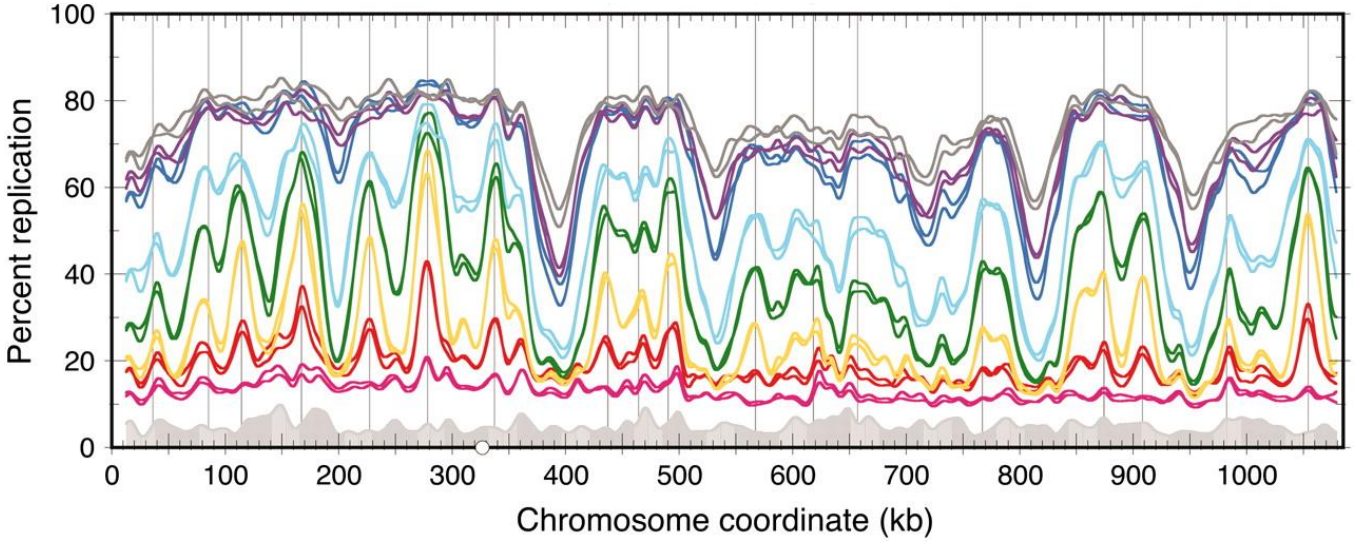


$$f(x,t) = 1 - \prod_{i=1}^{N} \left[1 - \Phi_i \left(t - \frac{|x - x_i|}{v} \right) \right]$$

global fork velocity

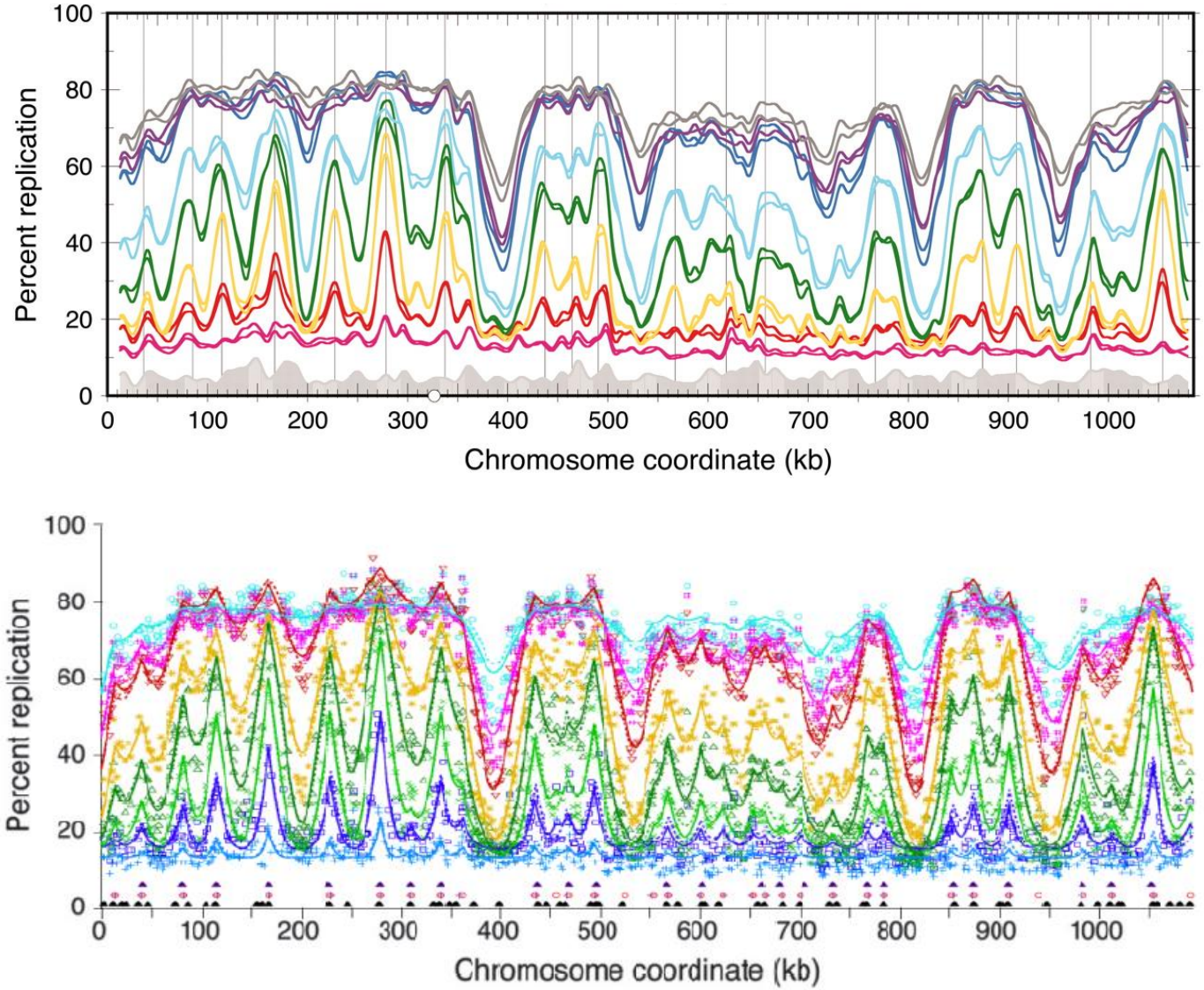
Result 1: fit

McCune 2008

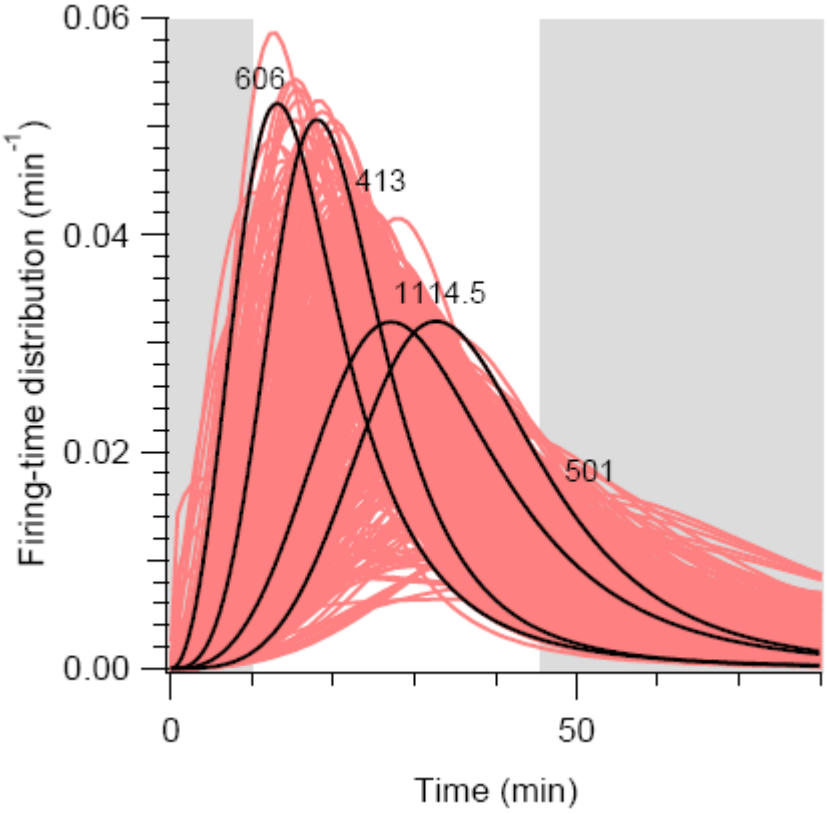


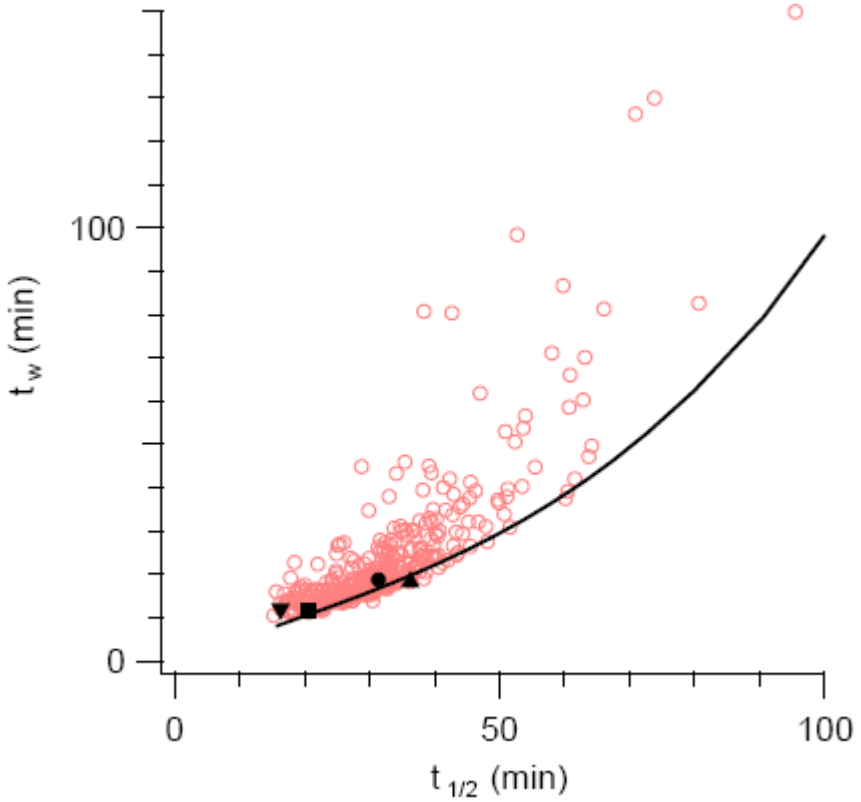
Result 1: fit

McCune 2008



Result 2: firing-time distributions





An idea

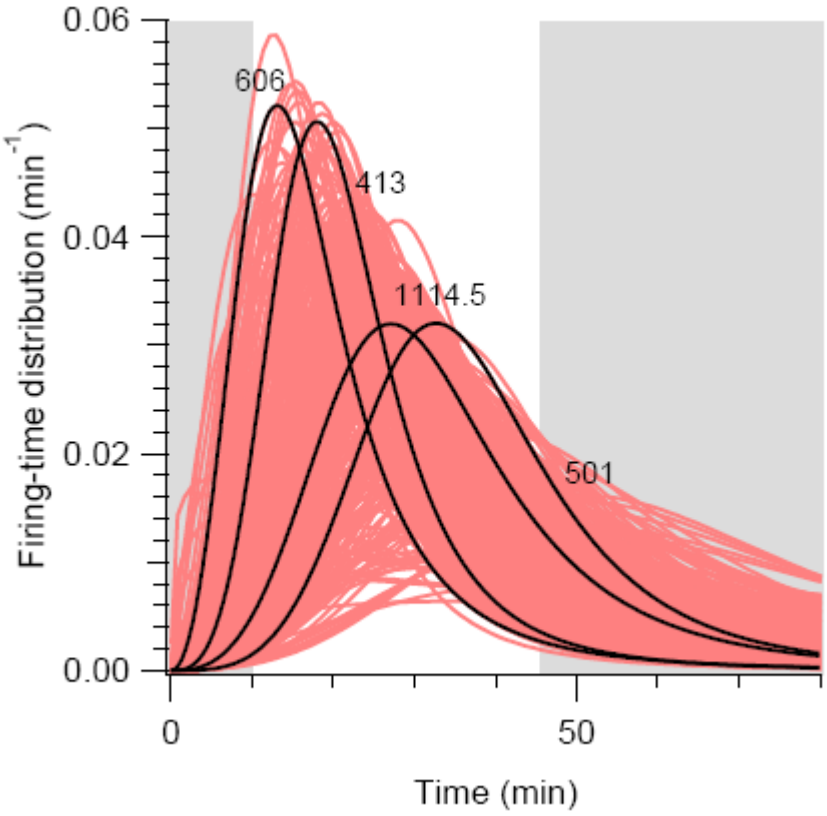
The number of MCM exceeds the number of ORC by a factor of 10– 100 in various organisms!

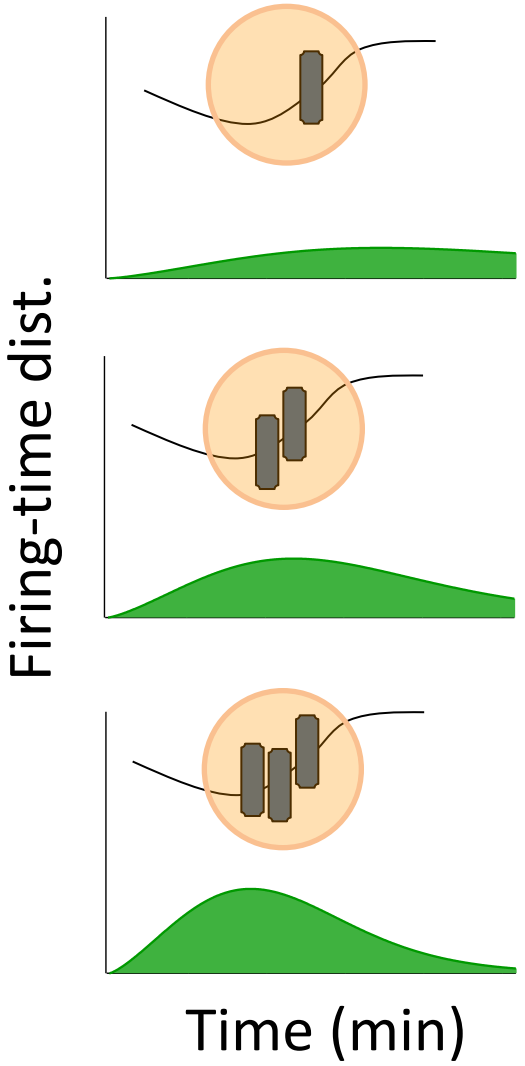
Hyrien 2003

Maybe…origins with lots of MCM fire early.

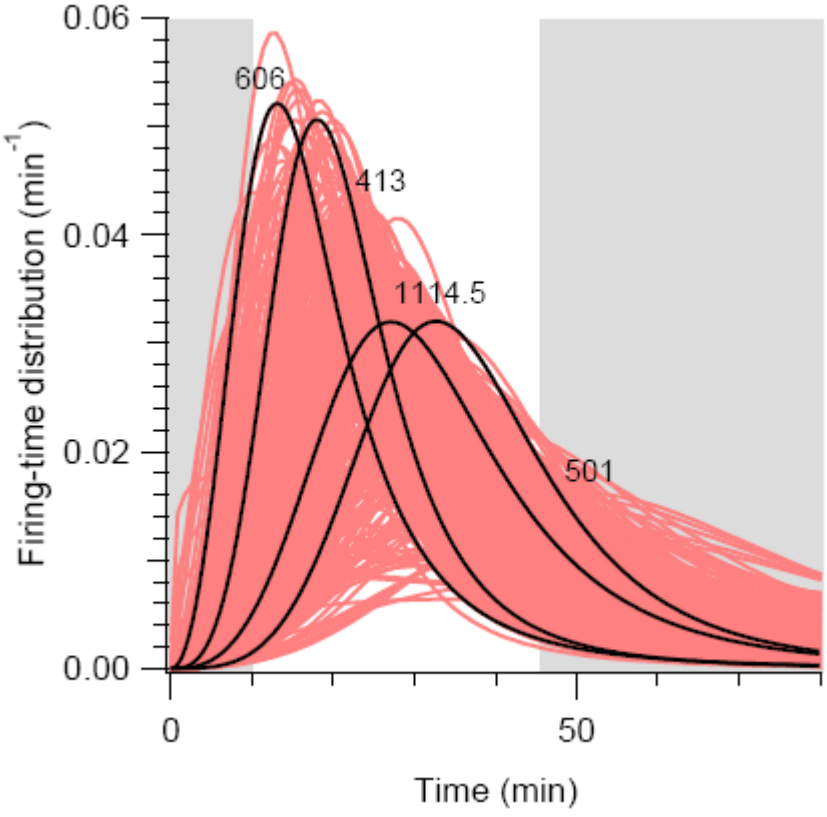
Nick

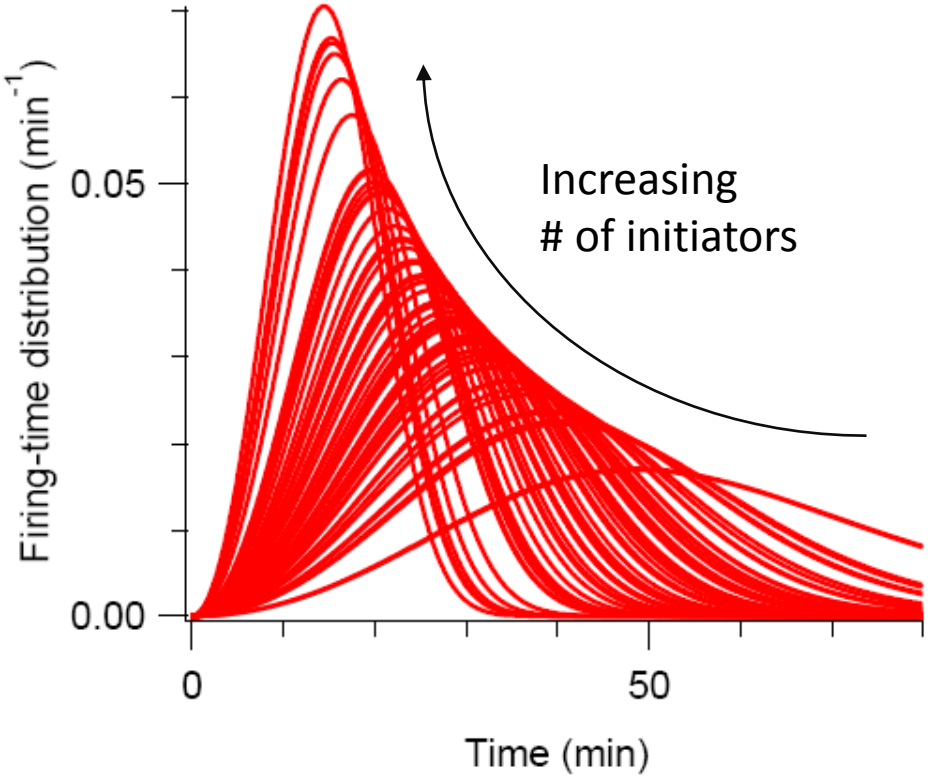
Multiple stochastic initiators





Multiple initiator model





Point of Views

More stochastic

- How to ensure precise firing time if needed?

Point of Views

More stochastic

- How to ensure precise firing time if needed?
- Give it lots of MCM

Point of Views

More deterministic

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Point of Views

More deterministic

- What counts the time and how?
- ????

More stochastic

- How to ensure precise firing time if needed?
- Give it lots of MCM

Conclusions

- DNA replication is a stochastic process
- We have developed a flexible, analytical model
- Timing needs not be from an explicit clock
  (contrary to most biologists' intuitions?)
- Timing can emerge from multiple stochastic initiators (MCM2 – 7)

Yang, Rhind, Bechhoefer, *MSB* 2010

Current work

- Probe MCM occupancy and other factors
- Other experimental setups & techniques
- Other organisms → universal program?

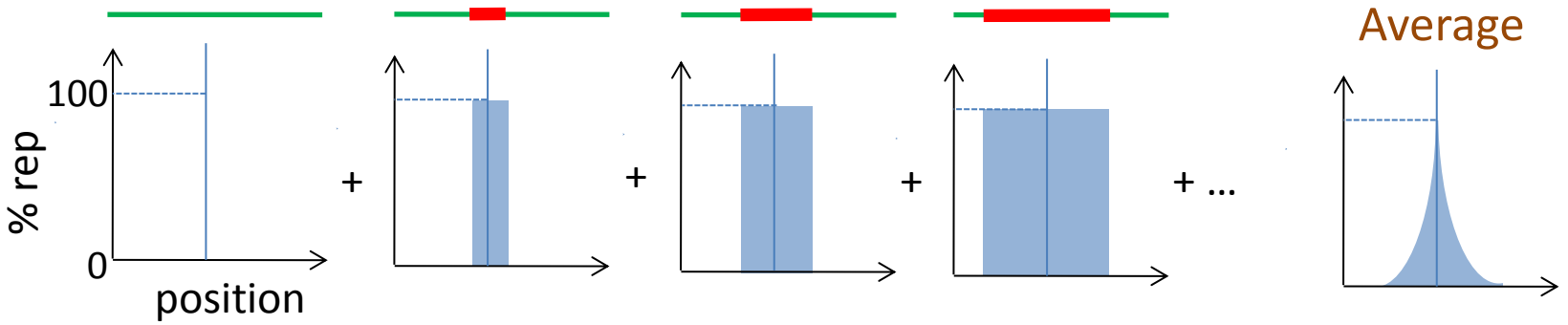
Molecular Systems Biology **6**:404 (2010)

Thank you!

Toy replication fraction profile

A culture of cells
T minutes into S phase

1 origin



Firing-time distribution