and replication forks required to complete replication increase drastically, and cells would require much larger amounts of replication factors such as DNA polymerase. The crossover occurs when the density of defects equals the density of firing origins in a defect-free genome.

Where do various living organisms lie on Fig. 3? For Table I, we combine measurements of interorigin distances with estimates of defect densities. Although we assume that the repair time is infinite, a more detailed analysis shows that a finite repair time merely reduces the effective value of λ by a minor amount [22]. Then, frog embryos, which have a simplified cell cycle that focuses on replicating as fast as possible, have $\lambda \approx 0.016$. Normal budding yeast cells and human somatic cells have $\lambda \approx 0.1$. The value for frog embryos is markedly lower than for somatic cells. Perhaps embryos need a larger ''safety margin'' because they lack the active checkpoint mechanism that mature cells have that can delay the cell cycle in order to repair DNA damage [23]. Next, a human cell mutant in which the DNA damage checkpoint response, DDR, has been inactivated but is otherwise normal gives a slightly higher λ, 0.22. All these values are well below the crossover at $\lambda \approx 1$.

We also include two cases that approach the crossover point. The first is from a specific region of the human genome (amplicon) that is known, qualitatively, to have more endogenous fork pauses [11]. The second is from DDR-inactivated cells where the Ras oncogene has been expressed, an event that is associated with increases in fork pausing and is a first step towards cancer [21]. Although there is unfortunately no direct data on the increase in defect density, we can estimate the value of λ via the measured reduction in interorigin distances and the model relation between interorigin distance shown in Fig. 3. These give $\lambda \lesssim 1$. In summary, embryos have $\lambda \approx 10^{-2}$, ordinary cells have $\lambda \approx 10^{-1}$, and cells with problems have $\lambda \approx 1$.

Correlation between fork velocity and origin spacing.—Experimentally, average fork velocities appear to be positively correlated with replication origin spacings [24]. Fork-velocity measurements are typically obtained from pulse-labeling experiments, where replication is observed by incorporating fluorescent markers during the synthesis