**Appendix for Pavani, Bonaiuti et al, “Epistasis, aneuploidy, and functional mutations underlie the evolution of resistance to induced microtubule depolymerization”**

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**Appendix Material and Methods:**

**Fixation dynamics in a Wright-Fisher (WF) model with mutations and selection.** A mathematical model to account for the number of population at fixation at the end of the experiment

This appendix reviews the derivation of the equations used to describe the fixation dynamics according to a WF model with mutations and selection.

We start by noticing that the evolutionary dynamics can be approximately split into two intervals. In the first interval, from the beginning of the experiment to sometime before Gr, we observed the fixation of the aneuploidy of chrVIII, but essentially no recurrent point mutations were detected. The second interval goes from this point to Gf, when we observe the fixation of all the recurrent point mutations. It seems therefore reasonable to assume that most of these mutations have emerged after the fixation of the chrVIII and before Gf, in a time interval of about 80 to 120 generations. These mutations have emerged on the aneuploid background, hence have an average selection coefficient s gen-1, as a result of their epistatic interactions with the extra chrVIII (see Fig 6A, columns 2 vs 5-6).



**Appendix Figure S1. Schematic of the fixation dynamics of beneficial mutations**. The time interval that goes from the fixation of disomy of chrVIII to the fixation of the beneficial point mutation is decomposed into two intervals (i) , during which no mutants have emerged yet, and consists in the time it takes to the successful mutation to emerge, and (ii) , the time from emergence of the beneficial mutation, appearing in the population of frequency (only one individual out of N), to the moment it reaches fixation ().

Hence, the total fixation time is assumed to be the sum of the duration of two time intervals: (i) , the time it takes to the successful mutation to emerge from the fixation of chrVIII, and (ii) , the time from emergence of the beneficial mutation to the moment it reaches fixation (i.e., an observed frequency ) (Figure Appendix 1 -- Figure A1). These two events can be described in mathematical terms as follows:

(i) the emergence of the successful mutant is modelled as a Poisson process with rate [2]

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where is the target size of the beneficial mutation, i.e., the number of nucleotide mutations that confer the same beneficial effect; is the constant population size; is the mutation rate per site, per generation and per individual and the selection coefficient of the beneficial mutation (in units of ). The observed number of distinct recurrent mutations that can potentially convey the same fitness effect,was used as a proxy for the mutational target size . The point mutation rate , was retrieved from the literature [3] (). Population size was between and (taking into account the experimental dilution factor -- between 1/3 and 1/7 -- and the measured population size (~107) ) while the value of will be inferred by matching the observed dynamics to the model expectation (see below).

Under these assumptions, the distribution of the emergence time reads

(ii) The time it takes to the beneficial mutation to go from an initial frequency to a final frequency (i.e., ) was described assuming a deterministic growth[[1]](#footnote-1), where the frequency x(t) of the beneficial mutations follows a logistic growth

Thus, this time interval, which fulfils the condition , reads

Given these two model ingredients, we estimated model parameters from experimental data as follows. We denote with the duration of the time interval between the fixation of ChrVIII and the detection of the beneficial mutations (. In order for a successful mutation to have reached fixation by the time , its first appearance in the population must have occurred in the time interval ]. The probability for a beneficial mutation to emerge in this interval reads

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We can match the observed dynamics to the model expectation by imposing the condition

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where is the observed fraction of wells (~12%) where, at the detection time (), the mutations had reached frequency . This condition is fulfilled with model parameters that satisfy the the following equation

We used this mathematical argument for the results shown in Figure A2. As can be seen, according to the WF model with mutations and selection, the average selection coefficient that can reproduce the observed number of wells (~12%) with recurrent mutations having reached a final frequency is in the range gen-1, in good agreement with the value measured experimentally ().

**Appendix Figure S2. The Wright Fisher model with constant population size can explain the observed fixation dynamics**. Average selection coefficient of the recurrent mutations that can reproduce the observed fraction of wells harbouring a recurrent mutation detected at frequency , here shown as a function of the time interval, in generations, between the fixation of the extra chrVIII and the fixation of the recurrent mutations (). The average selection coefficient was computed according to Eq. (1), assuming a mutation rate and . It was evaluated for two values of the population sizes (106 and 107, disks and squares, respectively) and several values for the final frequency ; the shaded area marks the region of values compatible with population sizes .

**Appendix References**

[1] Levy SF, Blundell JR, Venkataram S, Petrov DA, Fisher DS, Sherlock G. Quantitative evolutionary dynamics using high-resolution lineage tracking. Nature. 2015 Mar;519(7542):181-6.

[2] Kimura M. On the probability of fixation of mutant genes in a population. Genetics. 1962 Jun;47(6):713.

[3] Zhu YO, Siegal ML, Hall DW, Petrov DA. Precise estimates of mutation rate and spectrum in yeast. Proceedings of the National Academy of Sciences. 2014 Jun 3;111(22):E2310-8.

1. This choice is justified as in this case we expect the frequency of establishment, below which the dynamics is stochastic (dominated by drift, see [1]) is to be very close to zero, as since the selection coefficient is . Hence, the whole dynamics can be treated as a deterministic process. [↑](#footnote-ref-1)