METHOD ARTICLE

Model for *de novo* mutation propagation depending on paternal age at conception and associated neurological disorders [version 1; peer review: 1 not approved]

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Abstract

This paper presents a computational model for simulating the propagation of *de novo* mutations and paternal age effects in populations. The model uses data for paternal *de novo* mutation rates depending on age and demographic data such as age distributions, birth distributions versus age, varying life expectancy, and correlations with fertility. The number of paternal *de novo* mutations in children increases with the paternal age at conception. This might be of interest considering that the average paternal age has risen significantly in many societies throughout the last century. The model introduced below can superimpose and extrapolate different effects based on demographic dynamics. This includes the assessment of statistically associated neurological disorders in offspring, particularly IQ decay depending on the paternal age and other medical phenotypes which constitute paternal age effects. Yearly paternal mutation rates and correlations with paternal age were used to simulate both, *de novo* mutation propagation and probabilities for correlating conditions such as IQ decay. The extrapolated effect after several generations of persistently elevated paternal age appears to be drastic. To account for possibly mitigating factors, the paternal age effect has been super-positioned with the Flynn effect in simulated cases. The model automatically generates distributions for varying paternal ages, not just single cases, in convenient 3D distributions. The model simulates each person's individual reproductive incidents through a particle type approach which is more rigorous than insufficiently adaptive, continuum models based on partial differential equations. The model is not only applicable to humans and yields many valuable conclusions for a wide array of topics including the paternal age effect, correlations with intelligence, evolution, bottlenecks in evolution, as well as the role of *de novo* mutation.

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Keywords

paternal age, de novo mutations, IQ, demographic models

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Introduction

The DNA of a child is not exactly a composition of its father's and mother's DNA. *De novo* mutations, base pair changes, do occur during meiosis and throughout the parent's life, including in male gametes. It has been widely reported (Cannon, 2009; Gauthier & Rouleau, 2012; Kong *et al.*, 2012) that parental age at the time of conception is one factor contributing to a higher mutation rate. The number of *de novo* mutations rises particularly with the age of the father. Paternal *de novo* mutations have been found (Kong *et al.*, 2012) to increase by about 2.01 base pairs per year. For example, an age of 45 at conception entails an average 52.5 more *de novo* mutations in offspring than an age of 20.

Kong *et al.* showed that the father's age is the dominant factor in determining the number of *de novo* mutations in a child. By sequencing the genomes of 78 parent-child trios, Kong *et al.* found that the number of mutations increases (Gauthier & Rouleau, 2012; Kong *et al.*, 2012) with the father's age ($P = 3.6 \times 10^{-19}$) at an estimated rate of 2.01 mutations per year (standard error = 0.17). Some of Kong *et al.*'s rate dimensions imply a first-order relationship whereas others imply rather a zero-order dependency: i.e. respectively reporting an exponential increase with a doubling of paternal mutations every 16.5 years as well as a yearly rate of 2.01 *de novo* mutations. A first- or zero-order rate are of course two different propositions and, short off alleging a governing influence of a decay in DNA repair and replication, the formation of *de novo* mutations is proportional to the size of the genome, thus, implying rather zero order kinetics. Either way, for the reported comparison of two extrema of the age at conception the difference in order only affects the assessment of intermediate *de novo* mutation levels.

The paternal age effect describes the sensitivity of individual health to the average increase in *de novo* mutations in offspring due to elevated paternal age: e.g. 30 years of elevated paternal age resulting in ~60 base pair changes. As per Kong *et al.*'s reported standard error, the yearly *de novo* mutation rate has been considered as quasi linear and can thus be considered as of constant logarithmic order of magnitude throughout a man's life.

Regardless of the age at conception, *de novo* mutations present a constant limit to the conservation of DNA and a constant degrading effect on an organism's health, statistically detectable within one generation and even more significant when considered for historic time scales.

Increasing paternal age has been linked (Cannon, 2009) to a statistically detectable mental decline, an average IQ decline of six points for children of fathers aged 50 (at conception) compared to younger fathers, aged 20, as reported by Cannon. The correlation between *de novo* mutations and paternal age effect, with respect to the average IQ, might have been considered unexpected due to the logarithmic orders of magnitude separating the number of *de novo* mutations and the size of the entire human genome, as well as the small fraction of protein coding exon-DNA. A direct link to this statistical effect is nevertheless not only plausible, considering the influence of mutations in intron-DNA on the level of gene expression, but might also be negligent to discard considering the drastic outcome that this might entail for persistent trends of elevated paternal age. This paper presents a model that simulates the paternal age effect on IQ for societies and super-positions it with other effects: e.g. the Flynn effect, which is an increase in IQ points (Flynn, 1987) per generation, that has been found particularly during the 20th century's development of parenting and education. It has been disputed whether this is a temporal effect as the increases have been most prominent in data from well within the 20th century. Since then the average paternal age has continued to increase. The simulation presented in this paper super-positioned the Flynn effect with rising paternal age and yielded a good agreement with the recently observed halt or decrease of the Flynn effect (Sundet *et al.*, 2004).

The relevance of paternal age, that is, the relevance of a limited number of *de novo* mutations, for neurological and psychiatric disorders becomes consistent when considering not only rare mutations in protein coding DNA but also much more frequent genetic alteration in introns, which impacts protein expression, as evidenced by findings that confirmed the long suspected significant role of non-protein coding DNA in protein expression (Le Hir *et al.*, 2003; Nott *et al.*, 2003). Hence, increased random errors in DNA, due to increased paternal age, might plausibly yield statistical decreases in cognitive abilities.

The developed model can aid to assess these and:

1. couple *de novo* mutation accumulation simulations with correlations for IQ decline or probabilities for other health impacts statistically related to paternal age,
2. be useful for both, investigating genetic alteration depending on potentially relevant factors under investigation, such as environmental influences and demographic patterns in terms of reproduction,

3. assess dynamic distributions of neurological and psychiatric disorders (Gauthier & Rouleau, 2012) along multiple generations,
4. simulate the health of organisms and its interconnected dynamic properties during evolution and bottlenecks in evolution,
5. explain uncertainty in demographic models which heretofore didn't consider dependencies between these organism properties and reproductive patterns.

Methodology – modeling

A prerequisite to embarking some of the considerations mentioned above, is to recognize that long term developments of properties such as the average IQ belong to the vital interests of societies. Henceforth, even if cautioned that not all influences are yet quantified or even possible to quantify, potential decay factors, their impact potential and long-term impact should be anticipated and extrapolated, particularly assessing the order of magnitude of the potential change in the population's IQ distribution based on contemporary reproductive trends (here elevated paternal age across multiple generations).

The developed model simulates reproduction, mutations and IQ individually for each person in the simulated population. The initial age distribution as well as reproductive dynamics can be supplied to the model via demographic data. Reproduction occurs at a particular age with varying probabilities, depending on demographic input data. It is also possible to set a gender bias in the sex ratio of newborns. A for-loop checks every month whether the demographic data suggest reproduction and the associated probability. This has been embedded with a weighted random number ρ and normal distributed random number ρ_n . Children are born every month based on the set sex ratio and with added *de novo* mutations according to the paternal age. The IQ is then set randomized as per a normal distribution normed to the parental IQ, plus Flynn effect, minus paternal age effect as per its correlation with the accumulated *de novo* mutations. Simulated individuals die as per supplied demographic input data. Matrix M contains columns denoting age, gender, life expectancy, *de novo* mutations, and IQ. Reproduction occurs based on the relation $r_l + \rho > 1$ with $l = M_{i,l}$ where r is a vector containing the reproductive probability depending on age. If wanted, correlations between intelligence and fertility can be taken into account by involving the IQ in this relation.

The IQ is denoted in M for a newborn s and calculated with $\overline{IQ} = \overline{IQ}_{min} + \Delta IQ \frac{a_{max} - M_{i,1}/12}{\Delta a}$ and $M_{s,5} = M_{i,5}(1+F)(\rho_n\sigma + \overline{IQ})$.

$\overline{IQ}$ is the relative average IQ, Δa is the fertile age interval, σ the spread of the normal distribution, and F is the assumed IQ increase as per the Flynn effect.

Model simulating *de novo* mutations and paternal age effect on IQ

```
clear d y m f z i h b n s r t j c      %PATERNAL AGE EFFECT: IQ 9/10/15
d=30; y=d*10; m=y*12; f(y,31)=0; z=f; %decades, years & months; records f
i=2000;                                %initial population size i
h=70*12;                                %highest age in months h
b=1;                                     %gender ration b: boys/girls
n(1:h)=2.01;                             %dynamic de novo mutation rate n

for c=20:50                             %vary reproduction ages in loop
    clear M                               %Mij with j=1 age, 2 gender
    s=i;                                  %dynamic population size s
    M(1:s,1:4)=0;                         %Mij, j=3 de novo m., 4 lifespan
    M(1:s,4)=h;                            %lifespan in colum 4 of M
    M(1:round(b*s/2),2)=1;                 %gender (1: males, 0: females)
    M(:,1)=linspace(1,70*12,s); M=round(M); %even initial age distribution
    M(:,5)=1;                              %initial average IQ
    r(1:h)=0;                             %reset reproduction probability
```

```

r(c*12+1:(c+10)*12)=2.0/10; %fertile decade is varied
r=r/12; n=n/12; %convert yearly values to months
for t=1:m %simulate for all months m
    for j=1:s %simulate for all people s
        M(j,1)=M(j,1)+1; %people's aging
        if M(j,4)==M(j,1) %depart life after lifespan
            M(j,4)=-1; M(j,2)=0;
        end
        if M(j,2)==1 %if alive & male, then:
            M(j,3)=M(j,3)+n(M(j,1)); %collect de novo mutations
            if r(M(j,1))+rand>1 %reproduce per set probability
                s=s+1; %grow number of people
                q=.92+.08*(60-M(j,1)/12)/40; %age based Gauss f(IQ)
                M(s,5)=M(j,5)*1.05*(randn*.15+q); %assign random IQ
                M(s,1)=0; M(s,4)=h; %assign age & lifespan
                M(s,2)=round(b*rand); %gender as per gender bias
                M(s,3)=M(j,3); %inherit de novo mutations
            end
        end
    end
    if t/12==round(t/12) %record data yearly
        z(t/12,c-19)=sum(M(:,2))/b*2; %record population z & mean IQ
        f(t/12,c-19)=sum(M(:,2)'*M(:,5))/sum(M(:,2));
    end
end
end
end

```

The simulated cases shown in [Figure 1](#) and [Figure 2](#) below have the specifications: 1.) A population of 20,000; 2.) 300 years; 3.) Average number of children is 2; 4.) No gender bias concerning delivery of baby boys and girls is assumed but could be accounted for by setting a different value for the sex ratio b ; 5.) *De novo* mutation accumulation has been assumed to obey published data ([Gauthier & Rouleau, 2012](#); [Kong et al., 2012](#)).

Figure 1. IQ versus years after start of simulation and versus the decade of paternal reproduction. The start of the decade is varied from 20 to 50. The optimistic assumption of a continuous Flynn effect has been super-positioned.

Figure 2. IQ versus years after start of simulation and versus the decade of paternal reproduction. The start of the decade is varied from 20 to 50. The optimistic assumption of a continuous Flynn effect has been super positioned which yields very high IQs for young paternal ages after 300 y.

Life expectancy is of little relevance for the simulated results, considering that in most cases death occurs after the fertile age period.

A nonlinear *de novo* mutation accumulation rate, as plausibility due to changing cell division and DNA repair protein activity throughout life, can be used as already provided for by keeping y as vector. This can easily be incorporated with linear ratios (splines) between each data point yielding varying rates depending on age. The reproduction probability distribution can be set as per demographic data from any population of interest and represented as vector r . This particle type model illustrates that different effects can be conveniently superimposed. Furthermore, it allows to assess the order of magnitude of the problem as shown in the simulated cases where conception occurs in different paternal age intervals, starting with an interval from 20 to 30 and ending with an interval from 50 to 60. That means, 30 different reproductive patterns in terms of paternal age are simulated for comparison, the youngest assuming reproduction to occur between 20 and 30 and the oldest assuming paternal age at conception to be between 50 and 60.

Results and discussion

Currently the model is intended to assess the order of magnitude of the impact of elevated paternal age after multiple generations - not to do forecasting for average properties - since several input distributions, such as for reproduction, age, life expectancy and gender ratios, are set to constant values. The model simulates each individual and thus requires much more computational capacity than models relying on partial differential equations which average every constituent into a continuum. Therefore, if populations >1 million, that is, whole societies or populations, are to be simulated, then supercomputers might support practicable computational times. Several conclusions can be gleaned from the simulation illustrated in Figure 1 to Figure 4 and listed in Table 1.

Obviously, limits in the conservation of DNA are usually outpaced by evolution, mating patterns or might be masked by improved social, environmental, parenting, etc. conditions – particularly the later are difficult to model.

And heretofore, a constant decay of any health indicator has not been observed. Therefore, there might be a set of mechanisms that effect reproductive patterns and compensate for the about 2 yearly paternal random *de novo* mutations in inherited DNA. It is not possible for us to identify (e.g. possibly mating choice based on facial symmetry, intelligence, etc.) or quantitatively assess these mechanisms as rigorous as the underlying *de novo* mutations that they might be mitigating.

Figure 3. Illustrating uneven distributions for simulations of small populations due to the high impact of personal fate (compared to [Figure 1](#)).

Figure 4. Illustrating uneven distributions for simulations of small populations due to the high impact of personal fate (compared to [Figure 2](#)).

Table 1. Conclusions from model and simulation.

	Conclusions
1.	The correlation between continuous paternal accumulation of <i>de novo</i> mutations and intelligence has not been discovered before comparing different paternal age groups. Therefore, it might have been masked by other factors including reproductive patterns. To offset the paternal age effect, they must be sufficiently significant to constitute an uncertainty in various adjacent problems such as demographics.
2.	Demographics, reproduction, and the paternal age effect, that is <i>de novo</i> mutation levels in newborns, are coupled, with both influencing each other, as supported by recent findings (Arslan <i>et al.</i> , 2017).
3.	The model permits to elucidate highly interconnected patterns of organism health and reproduction in evolution scenario (not only for humans).
4.	The model (if run for small populations) indicates ill-posed, susceptible to random influences, behavior during evolutionary bottlenecks. This statistical particle model shows for the same initial conditions substantially varying outcomes, depending on the set of random numbers (for small populations, i.e. isolated communities or evolutionary bottlenecks).
5.	Investigated demographic distributions should be empirically supplied to the model, such as: Correlation of intelligence with fertility, correlation of other health indicators with fertility, correlation of <i>de novo</i> mutation levels in newborns with later fertility.
6.	To validate paternal age effect correlations, it is recommendable to include data from bioinformatics which detail affected genes' functionality, rather than just macroscopic demographic distributions.
7.	The effects of continuously elevated paternal age in society can be assessed, particularly with respect to the order of magnitude of the impacts, by super-positioning in simulations impacting and mitigating factors for investigated countries/regions.
8.	For example, the simulation returned that, even under the optimistic assumption of a never-ending Flynn effect, if super-positioned with the paternal age effect, then an average paternal age above 40 would lead to the long-term decline of the average IQ in society.

Nevertheless, considering the constant pace of *de novo* mutations and detectable associated statistical impact, these mechanisms might entail a similar imminent and substantial response in reproductive patterns. Interestingly, therefore, possibly spelling another uncertainty for demographic modeling.

The model also illustrates the ill-posed fate and predictability for small populations. If the simulated population is small, e.g. 2,000, then individual fate will cause an uneven surface or curve as in [Figure 3](#) and [Figure 4](#) below. [Figure 1](#) and [Figure 2](#) above were produced from simulations for 20,000 individuals and look more even. Bigger populations should be simulated, e.g. a few hundred thousand, to even out individual fate and further smooth the surface.

Conclusions

De novo mutations are accumulated all the time regardless of age at about 2 base pair changes per year, also in children conceived at young age. Mitigating mating choices and reproductive patterns are merely given less opportunity to outpace *de novo* mutations in case of elevated paternal age. Yet the impact of *de novo* mutations and the correlation between continuous paternal accumulation of *de novo* mutations and mild IQ decay has not been discovered before comparing different paternal age groups. Therefore, the effect appears to have been masked by mitigating factors which constitute an uncertainty in modeling. Hence, assessing the paternal age effect due to accumulating *de novo* mutations in offspring across multiple generations is prone to uncertainty short off an understanding of complex mating dynamics. Nevertheless, simulated cases illustrate the drastic outcomes of persistent elevated paternal age over multiple generations at already one logarithmic order. The model results illustrate highly interconnected patterns in organism health and reproduction in evolution scenarios (not only for humans). The model, if run for small populations, indicates ill-posed, susceptible to random influences, behavior during evolutionary bottlenecks. This statistical particle model shows for the same initial conditions substantially varying outcomes, depending on the set of random numbers for small populations, i.e. isolated communities or evolutionary bottlenecks. Investigated demographic patterns should be empirically supplied to the model, such as: Correlations of intelligence with fertility, correlations of other health indicators with fertility, correlations of

de novo mutation levels in newborns with later fertility. To validate paternal age effect correlations, it is recommendable to include data from bioinformatics, which detail affected genes' functionality, rather than just macroscopic demographic distributions. The effects of continuously elevated paternal age in society can be assessed, particularly with respect to the order of magnitude of the impacts, by super-positioning in simulations impacting and mitigating factors for investigated countries/regions. For example, the simulation returned that, even under the optimistic assumption of a never-ending Flynn effect, if super-positioned with the paternal age effect, then an average paternal age above 40 would lead to the long-term decline of the average IQ in society.

Software and data availability

The entirety of the model code is documented in the Methodology section. The code for plotting figures is documented in the Appendix. Input data such as population size and *de novo* mutation accrual rate are also detailed in the Methodology section. The model can be run on [MATLAB 9](#) or [Octave 4.2](#).

Appendix

Figure plot

```
%1st fig.: IQ function of t & age at start of decade of conception
figure('name','IQ function of t & age at start of decade of conception')
surf(20:c,round(y/2):y,100*f(round(y/2):y,:)) %(for 2nd half of t-span)
xlabel('1st year of decade of conception');
ylabel('years after start of simulation'); zlabel('IQ');
title('IQ function of t & age at start of decade of conception')
%2nd fig.: Average IQ after simulated period depending on age at conception
str=sprintf('IQ after %i years versus age at start of reproduction',y);
figure('name',str)
plot(20:c,100*f(y,:), 'o'); hold on
line(1:c-20+1)=100; plot(20:c,line,'red'); %initial average IQ comparison
title(str)
str=sprintf('average IQ of society after %i years',y);
xlabel('1st year of decade of conception'); ylabel(str);
```

Competing interests

No competing interests were disclosed.

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This paper is an interesting attempt to simulate paternal age distributions and associated population level outcomes of interest, such as the number of de novo mutations and cognitive ability (IQ), over generations. The paternal age distributions themselves are only of instrumental interest, the core aim of the model is to shed light on the population patterns in the outcomes under certain assumptions regarding the links between the outcomes and paternal age.

The simulations include effectively three steps, each increasing the level of complexity. The first step is to simulate the paternal age distributions. The second step involves linking paternal age to the number of de novo mutations. The third step calls for linking paternal age, or the number of de novo mutations, or both to the social outcome of interest, which in this paper is IQ.

Each of the three steps involves decisions. The first step of simulating paternal age is in principle straightforward as only demographic input is needed. The authors appear to assume that paternal age has increased throughout the last century. This however runs counter to existing research. For example, Arslan *et al.* (2017) document that average paternal age has increased in Sweden since 1970, but decreased from 1930 to 1970 and is today still lower than in 1880. It is easily forgotten that although ages at first birth rise, people also have fewer children on average, stopping earlier. Based on the simulations, the authors find that average paternal age over 40 years of age would lead to population level declines in IQ, even if the so-called Flynn effect would continue. This indeed is a result of the simulation. However, an average paternal age of 40 years is currently far beyond observable levels, and it seems to be bold speculation what might happen once such levels were reached.

The second step links paternal age to the number of de novo mutations. Existing research that is

cited in the paper (Kong *et al.*, 2012) provides numbers that can be used for this, although newer, larger studies should also be considered (Ségurel, Wyman, & Przeworski, 2014; Wong *et al.*, 2016). However, the authors do not cite work on evidence for contemporary evolutionary selection against genetic variants linked to education and presumably intelligence (Kong *et al.*, 2017; Marioni *et al.*, 2016).

The third step is perhaps the most challenging one. The authors assume a model that links IQ to the number of de novo mutations, without explicit link to paternal age. Implicitly, via a simulated link between parental age and de novo mutations, the model delivers a monotonic negative link between IQ and parental age. This, however, does not correspond to what is observed in the data (Arslan, Penke, Johnson, Iacono, & Mc Gue, 2014; Carslake, Tynelius, van den Berg, Davey Smith, & Rasmussen, 2017; Myrskylä, Silventoinen, Tynelius, & Rasmussen, 2013). Nor is the simulation code sufficiently clearly documented for us to understand how large a relationship with paternal age is actually assumed, and whether any non-genetic variation in IQ is allowed.

Research has predicted negative effects of de novo mutations on intelligence, because of theoretical accounts that the interindividual variation in intelligence is upheld by mutation-selection balance (Arslan, 2017; Penke, Denissen, & Miller, 2007) and empirical results linking de novo mutations to developmental disabilities (Deciphering Developmental Disorders Study, 2017) and rare genetic variants to intelligence (Hill *et al.*, 2017). Although the authors cite Arslan *et al.* (2017), they do not implement in their simulations that higher paternal age is still linked to lower offspring fertility in all populations we studied. By modelling one force, mutation, but not the potentially countervailing one, selection, as shown for paternal age by Arslan *et al.* (2017) and for education by Kong *et al.* (2012) and Marioni *et al.* (2016), they can obtain the result that intelligence decreases dramatically. Further, although the authors seem to be aware of intelligence-mortality and intelligence-fertility associations, they do not incorporate empirical estimates (Batty, Kivimäki, & Deary, 2010; Kolk & Barclay, 2017) into their model.

On a more technical side, the model either has some mistakes or is insufficiently documented. For example, it does not produce IQ values with a standard deviation of 15, as would be implicitly expected. Dead people seem to become female (this seems to be irrelevant to the results), and there is an oddity about age being linked to sex for unexplained reasons. Explicit and descriptive variable names, more comments, and making the simulated data available as a clearly labelled dataset would help with these problems.

To summarise, we think demographic predictions such as these are important but require more forethought and modelling complexity than provided here, especially when extrapolated hundreds of years into the future. Previous attempts (Woodley of Menie & Fernandes, 2016; Woodley of Menie, Sarraf, & Fernandes, 2018) have in our opinion (Arslan, 2017; Arslan *et al.*, 2018) also fallen short of addressing this complexity. While we think the current attempt should not be used to announce a future health and intelligence crisis, a revised and refined model could be useful. It should be calibrated with empirical parameters found in the literature and tested according to its ability to predict past time series of the intelligence distribution from parameters such as paternal age which both have been historically recorded in Scandinavian countries.

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- 19.

Is the rationale for developing the new method (or application) clearly explained?

Partly

Is the description of the method technically sound?

Partly

Are sufficient details provided to allow replication of the method development and its use by others?

Partly

If any results are presented, are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions about the method and its performance adequately supported by the findings presented in the article?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: paternal age, intelligence, demographics

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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