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Quantitative analysis of radiation-induced chromosome aberrations

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Abstract. We review chromosome aberration modeling and its applications, especially to biodosimetry and to characterizing chromosome geometry. Standard results on aberration formation pathways, randomness, dose-response, proximity effects, transmissibility, kinetics, and relations to other radiobiological endpoints are summarized. We also outline recent work on graph-theoretical descriptions of aberrations, Monte-Carlo computer simulations of aberration spectra, software for quantifying aberration complexity, and systematic links of apparently incomplete with complete or truly incomplete aberrations.

Ionizing radiation induces a rich variety of different chromosome aberrations. Simple aberrations, involving only two chromosome breaks (here considered as DNA double strand breaks, DSBs), and complex aberrations, involving three or more DSBs, are readily produced. Frequencies depend systematically on aberration type, chromosome size, dose, dose rate, radiation quality, and cell type. Such a situation, where extensive and diverse data have orderly quantitative interrelations, calls for modeling. In fact, mechanistic aberration models have long been used (reviews: Edwards, 2002; Hlatky et al., 2002; Natarajan, 2002; Savage, 2002). Current goals include analyzing biodosimetric signatures for different radiations, comparing different DNA repair/misrepair pathways, probing interphase chromosome geometry, and extrapolating data to low doses.

This review emphasizes chromosome-type, exchange-type aberrations – the case for which we have the most information. We outline aberration characterizations, proximity effects, classic mathematical approaches applicable primarily to simple aberrations, computer methods that can also handle the full spectrum of complex aberrations, systematic analysis of exchange complexity and apparent incompleteness using new software, transmissibility, and relations of aberrations to other damage.

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Characterizing aberrations and their formation

An exchange-type aberration, resulting from misrejoining of DSB free ends, can be described either by its observed final pattern at metaphase (e.g. Fig. 1A) or by a possible formation process starting earlier (Fig. 1B). Both description methods have advantages and drawbacks, both have often been used, and both have been clarified by recent quantitative modeling.

Observed final patterns depend on the protocol used, for example mFISH (Greulich et al., 2000; Loucas and Cornforth, 2001; Anderson et al., 2002; Durante et al., 2002) or solid staining. Systematic comparison of results obtained with different protocols is important. Some universal description method will be needed to construct radiation cytogenetic databases. Strong similarities between "detailed" ISCN nomenclature (ISCN, 1995) and mPAINT (Cornforth, 2001) suggest such a method (Sachs et al., 2002). The key idea is that protocols differ mainly in the way they describe chromosome segments; all have some way to identify misrejoinings. Applied to whole-chromosome painting, the unified method is very similar to mPAINT – examples are given in the caption to Fig. 1 and in the subsection on cycle structures below. However, the method is compre-

hensive, being applicable also to solid staining, G-banding, FISH, armFISH, multicolour banding, synteny based on specifying the order of oriented genes (Pevzner and Tesler, 2003), DNA sequencing, etc. It can be used for apparently incomplete patterns.

Actually, most current modeling concerns aberration formation processes (e.g. Fig. 1B), rather than just final patterns (e.g. Fig. 1A), even though formation processes are harder to observe experimentally, and this approach also has a long history (Savage, 1998). An aberration formation process can be described systematically with a unified "aberration multigraph" that shows DSB locations in the genome, the misrejoining process, and the final configuration of rearranged chromosomes (Sachs et al., 2002).

One important biophysical pathway of aberration formation is breakage-and-reunion (Fig. 2A), presumably based on non-homologous end joining. A one-hit pathway based on homologous repair/misrepair also sometimes occurs (Fig. 2B). A third, exchange-first, pathway has been suggested (Fig. 2C). We believe there is strong evidence from aberration spectra, dose-response relations, and analyzing enzyme action that, for irradiation of mammalian cells during G_0/G_1, breakage-and-reunion is the dominant pathway (Sachs et al., 2000b). This view is controversial (Goodhead et al., 1993; Cucinotta et al., 2000; Edwards, 2002). Recently, another one-hit pathway has been suggested, involving exchanges localized at transcription factories (Radford, 2002).

Proximity effects and chromosome geometry

Whatever the pathway, an exchange requires spatial juxtaposition of two or more genomic loci (Fig. 2). Consequently, there are "proximity effects", i.e. influences of interphase chromosome geometry and motion on aberration frequencies, espe-

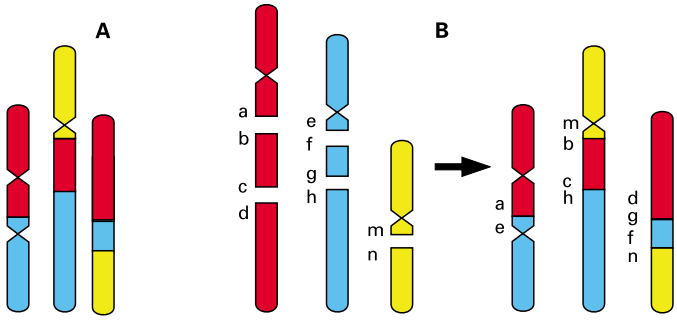

Fig. 1. A complex aberration. (**A**) schematically shows an observed mFISH pattern with at least five misrejoinings. Descriptors are (red′(::blue′) (yellow′::red::blue) (red::blue::yellow). Here: parentheses indicate rearranged chromosomes; primes denote centromeres; and, as in ISCN (1995), double colons are used for required misrejoinings. Assuming no cryptic DSBs, there are four possible aberration formation processes. One of these four is shown in (**B**); the other three differ by inversions switching b with c and/or f with g on the right.

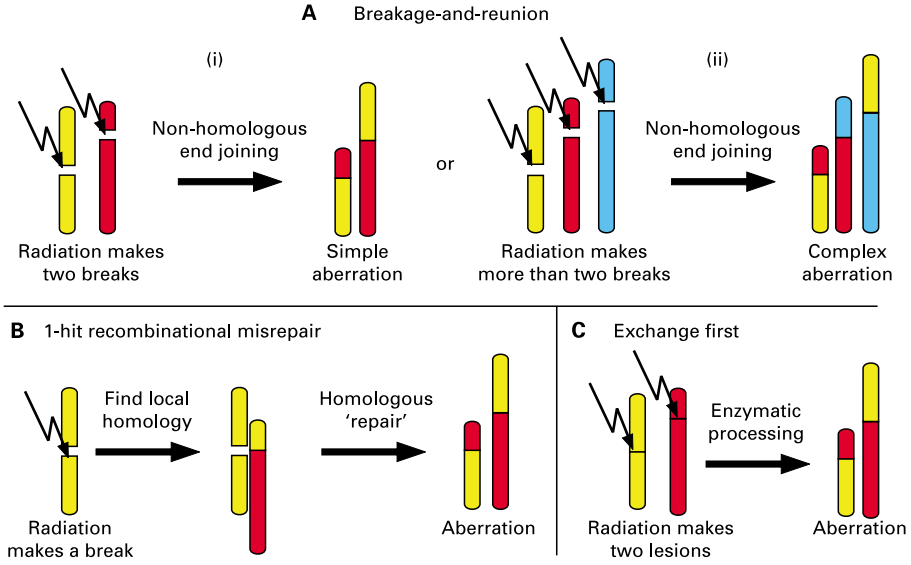

Fig. 2. Aberration formation pathways (review: Hlatky et al., 2002). In the breakage-and-reunion pathway (**A**), radiation makes DSBs, each of which has two free ends. Each free end then rejoins with another free end, either restituting (i.e. restoring the original DNA sequence apart perhaps from some comparatively small scale changes) or misrejoining, presumably by non-homologous end joining. In a misrejoining, the two free ends of one DSB can either act in concert (**Ai**), or misrejoin independently, at different genomic locations (**Aii**). Due to the possibility of independent misrejoining, complex aberrations can arise readily and very complex aberrations can result. (**B**) indicates a different pathway. One essential difference is that a single radiation-induced DSB can initiate an exchange, presumably made by enzymatically-mediated homologous misrepair as shown. In the usual versions of this pathway, DSB free ends are constrained to act in concert during the recombinational event, as shown in panel **B**. This constraint leads to model predictions of a much smaller proportion of complex aberrations relative to simple ones than in the breakage-and-reunion case. It also limits the type of aberrations that can arise. (**C**) shows the Revell-type exchange-theory pathway. As in **A**, a single radiation-induced lesion cannot by itself induce an exchange. As in **B**, free ends of the same lesion are constrained to act in concert, restricting the type and frequency of complex aberrations.

cially important in conjunction with DSB clustering (reviewed in: Sachs et al., 1997a, 1999; Kreth et al., 1998). Conversely, the surprisingly rich aberration spectra uncovered by current techniques, when combined with biophysically-based computer modeling, help characterize large-scale interphase chromatin architecture.

When analyzing proximity effects chromosomes are often represented by random walk or polymer models (Hahnfeldt et al., 1993; Sachs et al., 1995, 2000a; Münkel et al., 1999; Ostashevsky, 2000; Ottolenghi et al., 2001; Andreev and Eidelman, 2002; Holley et al., 2002) many of which are coarse-grained. However, very detailed models (e.g. Friedland et al., 2003) are also available.

Most proximity results on radiogenic aberrations (review: Hlatky et al., 2002) are consistent with the picture obtained by imaging (review: Parada and Misteli, 2002), wherein chromosomes are mainly confined to territories and interchromosomal interactions involve mainly territory surfaces or perhaps loops protruding far from the home territories. However, observation of highly complex aberrations suggests more intermingling of chromosome territories than does direct imaging. Frequencies of specific mFISH color junctions in irradiated cells (Cornforth et al., 2002b) indicate considerable randomness in chromosome-chromosome juxtapositions, superimposed on more systematic chromosome spatial locations suggested by other methods (e.g. Boyle et al., 2001; Cremer et al., 2001).

Classic quantitative aberration models

We review three mechanistic approaches which have long been useful, primarily for analyzing simple aberrations detected at the first metaphase after irradiation.

Randomness model (Savage and Papworth, 1982)

The basic version of this model makes two assumptions: (a) At low LET DSBs occur independently with a probability for any part of the genome proportional to genomic content (averages over regions appropriate for the lower limit of resolution of conventional cytogenetics, having order of magnitude of 5 Mb, are involved); (b) DSB free end misrejoining partners are random. These two randomness assumptions have many testable implications. For the special case of just two DSBs (i.e. pairwise misrejoining of four free DSB ends), the formalism predicts, among other things: (a) equal frequency of asymmetric simple aberrations (dicentrics, centric or acentric rings) and their symmetric counterparts (translocations, peri- or paracentric inversions); (b) the Lucas formula (reviewed in Sachs et al., 2000b) for the fraction of simple translocations that involve a color junction; (c) if proximity effects were negligible the ratio of simple dicentrics to simple centric rings for a human genome would be ~ 87.

Often, predictions of the Savage-Papworth formalism approximate the data well (reviewed in Johnson et al., 1999; Sachs et al., 2000b). However:

- Painting results (e.g. Knehr et al., 1996; Cigarrán et al., 1998) suggest taking the "effective length" (Savage, 1991) of a chromosome as approximately $\propto$ (genomic content)$^{2/3}$ rather than $\propto$ (genomic content) to avoid systematically over-estimating the participation of larger chromosomes (reviewed in: Wu et al., 2001; Cornforth et al., 2002b). It has been suggested that this dependence of effective length on genomic content may be due to interchanges involving primarily chromatin at territory surfaces.
- There is evidence for specific deviations from randomness due to variations in chromatin structure (reviewed in Natarajan, 2002; Obe et al., 2002). It would be of interest to study if these can be related to the putative hot spots recently suggested in comparative genomics (Pevzner and Tesler, 2003).
- Assuming randomness strongly underestimates intrachanges relative to interchanges. Long ago, Savage and Papworth identified proximity effects as the explanation: chromosome localization in territories means a pair of DSBs on one chromosome is much more likely to misrejoin than a pair of DSBs randomly located in the genome (reviewed in Hlatky et al., 1992).
- At high LET, the spectrum of exchange-type aberration is expected to be different due to DSB clustering and proximity effects (Brenner et al., 1994; Chen et al., 1997; Sachs et al., 1997b; Ballarini et al., 2002; Holley et al., 2002). A different spectrum is indeed observed in vitro: there is a higher frequency of complex aberrations compared to simple ones; higher frequencies of aberrations involving several exchange breakpoints within the same chromosome; and perhaps more incompleteness (e.g. Sabatier et al., 1987; Griffin et al., 1995; Knehr et al., 1999; Boei et al., 2001; Fomina et al., 2001; Durante et al., 2002; Anderson et al., 2003; George et al., 2003; Wu et al., 2003a, b). Because of such tell-tale differences, retrospective biodosimetry should eventually be able to identify the type of radiation as well as the dose received. Whether there is a pronounced LET dependence of interchange/intrachange ratios has been quite controversial (e.g. Sachs et al., 1997a; Bauchinger and Schmid, 1998; Savage and Papworth, 1998; Schmid et al., 1999; Deng et al., 2000; Boei et al., 2001; Hande et al., 2003).
- When more than two DSBs are involved, and at high LET, Monte Carlo approaches, discussed below, are considerably more convenient than the randomness formalism.
- We predict that proximity effects should lead to an excess of rings compared to inversions. The reason is that the DSB free ends at the opposite ends of a chromatin segment (e.g. b and c in Fig. 1B) not only have a bias toward being close together when formed (because they are on the same chromosome) but have an additional bias for staying close together. Even if there is considerable motion of chromosome fragments, the two free ends will remain connected by the chromatin between them, and this constraint tends to favor ring formation. Modern protocols should make it possible to check this prediction, especially for the case of centric rings vs. pericentric inversions.

LQ dose-response estimates for simple aberrations

The theory of dual radiation action, TDRA (Kellerer and Rossi, 1978), gives the following linear-quadratic (LQ) formula

for the dependence of aberration frequency Y on total dose D and dose-rate R(t):

$$(A)\ Y = \alpha D + G\beta D^2,$$

where

$$(B)\ G = \frac{2}{D^2}\int_{-\infty}^{\infty} dt \int_{-\infty}^{\infty} dt'\ R(t)K(t-t')R(t'), \text{ with } (C)\ K(s) = \exp(-\lambda s). \qquad (1)$$

Here pairwise misrejoining of DSBs and mono-exponential restitution with rate constant $\lambda \geq 0$ are assumed. G applies to low dose-rate and/or fractionated irradiation, generalizing the Lea-Catcheside factor (reviewed in Sachs and Brenner, 2003); $G \leq 1$ and for a single acute dose G = 1. TDRA also expresses the LQ coefficients α and β mechanistically, in terms of an energy proximity function, a target proximity function for chromosomes, and a distance dependent interaction probability (Kellerer and Rossi, 1978). When supplied with these characterizations of α and β, Equation 1 very neatly encapsulates four key factors – radiation track structure, chromatin geometry, repair, and misrepair. Consequently it remains quite useful (e.g. Sachs et al., 1997a; Radivoyevitch et al., 2001) despite having limitations, such as ignoring complex aberrations, that have been uncovered and ameliorated by later formalisms. In biodosimetry (Blakely et al., 2002), LQ approximation is still central (reviewed in: Bauchinger, 1998; Kodama et al., 2001; Tucker, 2001; Edwards, 2002). Equation 1 with $\lambda \sim 1$ per hour often gives reasonable approximations to observed direct dose rate effects (e.g. Cornforth et al., 2002a; review: Lloyd and Edwards, 1983).

Reaction rate models for simple aberrations

"Reaction rate" biophysical models track time development, using the formalism (Erdi and Toth, 1989) of deterministic or stochastic chemical mass action kinetics; they are special cases of dynamic equations for genetic regulatory networks and metabolic control (de Jong, 2002). Many reaction rate models for simple aberrations have been investigated over the years (review: Sachs et al., 1997c). Recent examples include saturable repair models quantifying the mechanism shown in Fig. 2B (Cucinotta et al., 2000) and the two-lesions-kinetic (TLK) model, which allows for biphasic repair kinetics corresponding to two different kinds of DSBs (Stewart, 2001). Each deterministic reaction rate model has a corresponding stochastic version (e.g. Albright, 1989; Hahnfeldt et al., 1992; Radivoyevitch et al., 1998) that is computationally more involved, but is actually simpler from a conceptual point of view, is more accurate in many cases (especially at high LET), and can analyze statistical cell-to-cell fluctuations.

Reaction rate models for simple aberrations predict approximately LQ behavior (Equations 1A and 1B) at low and intermediate doses or dose rates (reviewed in: Guerrero et al., 2002), and to date their main application has been interpreting LQ parameters mechanistically. In most aberration studies (unlike many DSB studies) the LQ approximation to a reaction rate model is often adequate. For aberrations formed by high acute doses of low LET radiation (e.g. Sasaki, 2003), neither current reaction rate models nor LQ approximations are accurate, mainly because complex aberrations become so important.

Most radiobiological reaction rate equations ignore proximity effects – they use well-mixed instead of diffusion-limited chemical kinetics. Simple approximations to proximity effects can be incorporated by assuming "interaction sites" – a number of different, non-interacting regions in the nucleus of a cell (e.g. Radivoyevitch et al., 1998).

Computer modeling

Monte Carlo models of aberration formation

More recently, virtual experiments obtained from Monte Carlo simulations have been used to refine the approaches described in the previous section. The simulations are probabilistic, with a computer in effect "rolling dice" to give extremely detailed output. For example, for acute low LET irradiation, CAS (chromosome aberration simulator) software (reviewed in: Sachs et al., 2000a) starts by determining the locations of DSBs on one copy of chromosome 1 in one cell at random, using a random number generator. The other 45 chromosomes are then treated similarly, taking into account their DNA content. Restitution or misrejoining for the DSB free ends according to any of the aberration formation pathways (Fig. 2) is next simulated, as a discrete-time Markov process, taking proximity effects into account. Specifying the relevant scoring protocol (for example mFISH) then determines a simulated karyotype. Iterating, thousands or millions of metaphases are simulated, each with its own aberration pattern. The results can then be compared to experimentally observed aberration spectra and dose-response relationships

This probabilistic approach systematically emphasizes dominant processes and likely outcomes, appropriately discounting, without completely ignoring, minor formation pathways and many possible but unlikely aberration types. Complex aberrations can be simulated in complete detail, as is relevant, for example, to analyzing aberration spectra as biomarkers of radiation quality.

CAS has been applied primarily to low LET aberrations, though alpha particles have also been analyzed (Chen et al., 1997). Other programs for chromosome breakage and misrejoining have been developed (e.g.: Friedland et al., 2001; Ottolenghi et al., 2001; Andreev and Eidelman, 2002; Holley et al., 2002). These incorporate high LET radiation tracks more realistically and thoroughly but give less systematic descriptions of complex aberrations. A Monte Carlo approach by Moiseenko and coworkers (review: Edwards, 2002) has the advantage of tracking actual time dependence, instead of merely a sequence of steps.

Cycle structure: quantifying aberration complexity

A complete exchange-type chromosome aberration formation process has a cycle structure (Bafna and Pevzner, 1996; Sachs et al., 1999) specifying DSB numbers for separate irreducible reactions involved. For example, a simple aberration is formed by a reaction involving two DSBs, i.e. a 2-cycle c2; Fig. 2Aii describes a 3-cycle c3; Fig. 1B involves two separate reactions, one involving two DSBs (namely cd and gh) and the other involving three DSBs, so the cycle structure is c2+c3; etc.

An observed aberration pattern is often compatible with many different aberration formation processes, having various cycle structures; then the structure with the shortest cycles is designated "obligate" (Cornforth, 2001; Levy et al., 2003). For example, there are four possible five DSB processes for making the final pattern shown in Fig. 1A. The process shown in Fig. 1B has the obligate cycle structure, c2+c3, but each of the other three processes has cycle structure c5, indicating a single more complex exchange in each case.

As the number of misrejoinings required by the observed pattern grows to ~10 or more, the number of compatible processes becomes so large that recently developed software (available freely on the internet: Levy and Sachs, 2003) is needed to analyze cycle structures. For example, consider the mFISH pattern (1′::3::2′) (4::1) (2::3′) (3::1′::4′) (1::1) (:1:) (:2::1:). Here parentheses enclose different rearranged chromosomes, numbers indicate colours, primes denote centromeres, and double colons denote required misrejoinings; (:1:) and (:2::1:) denote rings. Assuming no cryptic misrejoinings, the software demonstrates 1,152 possible formation processes; 640/1,152 ~ 55.6% have cycle structure c10; only 16/1,152 ~ 1.4% have the obligate cycle structure c2+c4+c4. This example illustrates a general point – assuming obligate cycle structures tends to underestimate aberration complexity. For the more complex pattern (1′::3::2′) (2::1) (2′::3′) (3::1′::2′) (1::1) (2::2) (:1:) (:2::1:) there are 20,736 processes with 11 misrejoinings. Only 32/20,736 ~ 0.15% have the obligate cycle structure c2+c3+c3+c3 but 10,368/20,736 = 50% are 11-cycles c11. Such enumeration of cycle statistics can be replaced by Monte Carlo sampling, useful mainly for patterns so complex that >1,000,000 processes are possible.

Apparently incomplete aberration patterns

Many observed aberration patterns appear incomplete, either because some DSB free ends have actually failed to rejoin or, more often, because some segments are cryptic, where the difference between these two cases can be analyzed using telomere probes (reviewed in: Boei et al., 2000; Fomina et al., 2001; Loucas and Cornforth, 2001; Holley et al., 2002; Wu et al., 2003b). In complicated situations it may be difficult to relate apparently incomplete patterns to complete or truly incomplete aberrations (Cornforth, 2001). Algorithms have now been developed to handle this problem systematically for any whole-chromosome painting protocol (e.g. mFISH). In brief, first consider colours one at a time, setting T = (apparent telomeres) and C = (centromeres involved), with C > 0. For every colour with T < 2C, add to the observed pattern 2C-T "cryptic terminals" – small acentrics with one telomere and the other end either unrejoined or misrejoined. For every colour with T > 2C, consider T-2C apparent telomeres as actually being DSB free ends instead. Interrelations among complete, apparently incomplete but truly complete, and truly incomplete aberrations can then be methodically worked out as follows. One considers pairwise misrejoinings among the free ends introduced in the steps just described for T < 2C or T > 2C to get a complete pattern, or considers some of these free ends as unrejoined, corresponding to true incompleteness. Free software (Levy and Sachs, 2003) is available for complicated cases. Probabilities, e.g. for cycle structures, can be systematically assigned.

Cell proliferation and aberration transmissibility

It is important to analyze the behavior of aberrations, and of cells that contain them, at mitosis. The main quantitative formalism (Braselmann et al., 1986) extends a model of Carrano and Heddle. The formalism involves parameters defined in terms of behavior at the first post-irradiation cell division in vitro. One parameter is W, the probability that a simple dicentric allows viable daughters; another is the acentric transmissibility parameter T, with 2T specifying the probability that a cell with an acentric transmits at least one copy of the acentric to one or the other daughter cell. For human lymphocytes approximate values W = 0.42 and T = 0.41 were measured (Bauchinger et al., 1986). This approach has been generalized to more complex aberrations, to multiple aberrations, to later metaphases, and to in vivo situations (reviewed in: Lucas, 1999; Gardner and Tucker, 2002; Vázquez et al., 2002). However, chromosomal instability occurring many cell generations after irradiation (reviews: Lorimore and Wright, 2003; Morgan, 2003) needs additional quantitative modeling.

Relating aberrations to other endpoints

Recent results suggest that most total-gene or multi-exon deletions in standard mutation assays may be formed by essentially the same misrepair processes as exchange-type aberrations (reviewed in: Costes et al., 2001; Friedland et al., 2001; Wu and Durante, 2001; Singleton et al., 2002). Also for many cancers there are associations to specific exchange-type chromosome aberrations (Mitelman et al., 2002) which are causative or at least pathognomic in at least one case (CML; reviewed in Radivoyevitch et al., 2001). However, exchange-type aberrations differ significantly from many other radiobiological endpoints in that the aberrations always require more than one DSB (Fig. 2). At low LET for an acute dose of several Gy, most clonogenic lethality may be due to exchange-type aberrations such as dicentrics and rings. But for lower doses and for low dose rates, such aberrations contribute less to lethality than do other, smaller-scale lesions, involving only one track and presumably involving at most one DSB (Sachs et al., 1997c).

Discussion: conclusions and challenges

Studying aberrations with modern computational biology tools helps elucidate the underlying biophysical repair/misrepair mechanisms and interphase chromosome geometry. Mechanistic extrapolations to low doses, modeling aberration transmissibility in vivo, and modeling chromosomal instability are currently drawing considerable attention. Significant future challenges also include:

- Modeling chromosome aberration spectra, including intrachange size spectra, as fingerprints of radiation quality.
- Combining detailed track structure models with more realistic models of chromosome geometry, of cell nucleus architecture, of chromosome motion, and especially of DSB misrejoining.

- More systematic modeling of chromatid aberrations (compare Sipi et al., 2000).
- Extending PCC models (e.g. Wu et al., 1996), important because the process of aberration formation, rather than just the final configuration, is central.
- Quantitative models of other large-scale genome alterations, e.g. duplication and aneuploidy as occur in tumor cytogenetics, telomere fusions as suggested by ZooFISH in comparative genomics, etc. Closer integration of radiation cytogenetics with these other fields is needed.
- Importantly, clarifying the biological significance of aberrations compared to more frequent forms of damage such as point mutations – does the large-scale nature of the genome alteration entailed in an aberration lead to especially important phenotypic changes, or are aberrations merely easier to observe?

There is still a lot to learn.

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